Methanolysis, Acetolysis, and Rearrangement of *ortho*-Substituted Phenyl Acetates

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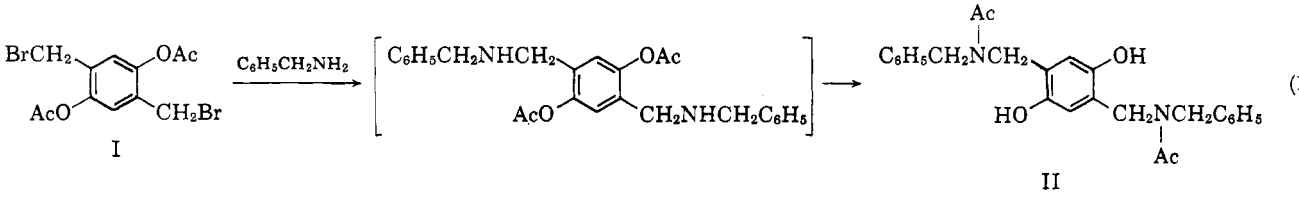
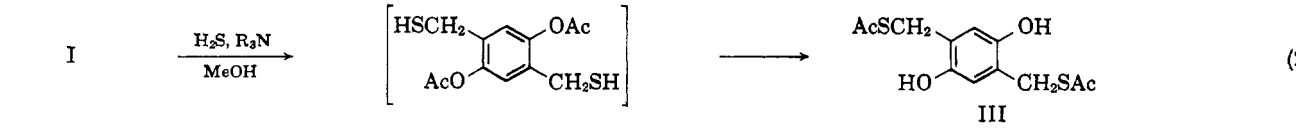
Received July 16, 1964

Methanolysis, acetolysis, and acetyl rearrangements of certain phenyl esters are reported. A common intermediate is suggested in these reactions.

In our study of certain phenyl esters we have encountered three types of reactions which have sufficient features in common to suggest a common reaction mechanism. The first such reaction involves acetyl rearrangements of the O → N, O → S, and O → O′ types, as shown in eq. 1–3. In each case we suppose that the products arise from the cyclic intermediate VI. Many examples of OAc ⇄ NAc and OAc ⇄ O′Ac are known[1] and cyclic intermediates have been suggested. The OAc → SAc rearrangement shown



(1)



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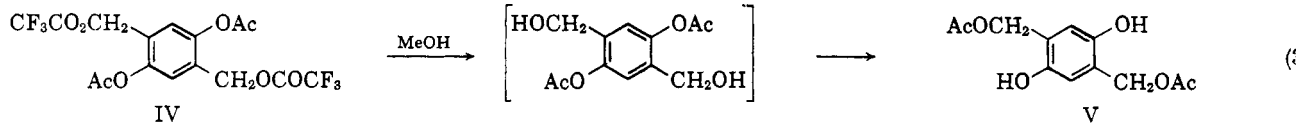
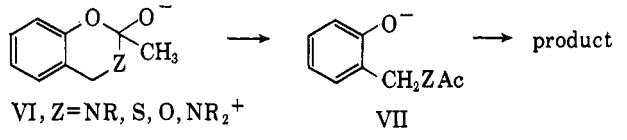


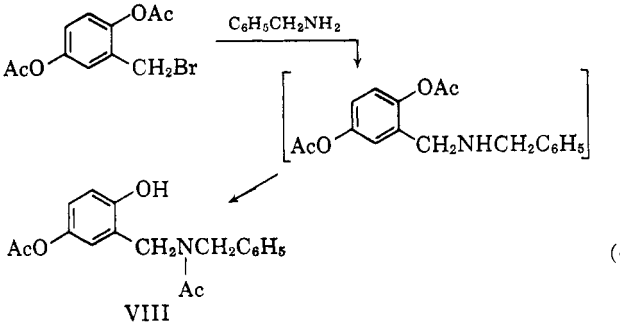
(3)

in eq. 2 is less well known and usually occurs in the reverse direction (SAc → OAc).[2] The unusual direction of opening of VI (Z = S) reported here is apparently due to the formation of a phenoxide anion. There is, for example, an intermolecular analogy with the reported reaction of ethylmercaptide with phenyl formate and acetate to yield ethyl thiolformate and ethyl thiolacetate, respectively.[3]

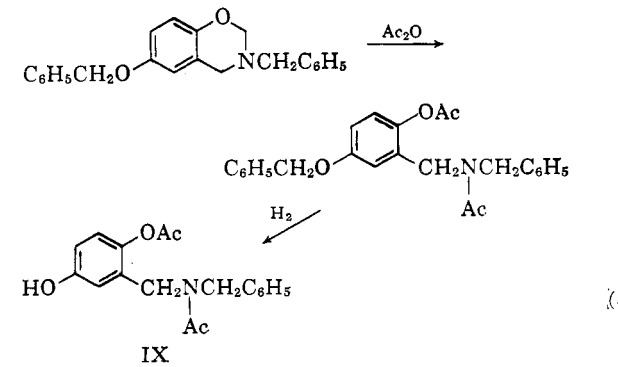


Intermediate VI requires an *ortho* arrangement for the participating groups and results in the specific rearrangement shown in eq. 4. The structure of the product, VIII, was proven by elemental analysis, infrared spectroscopy, and by preparing the isomeric compound, IX, as shown in eq. 5.

The influence of acetyl migration on the course of reaction is well demonstrated by the reaction of 2,3-bis(bromomethyl)hydroquinone diacetate with amines (eq. 6). Thus, although morpholine gives the expected quaternary salt, attempts to obtain ring closure with benzylamine failed and gave instead an amide, which quaternization showed still to contain an active halogen.



(4)

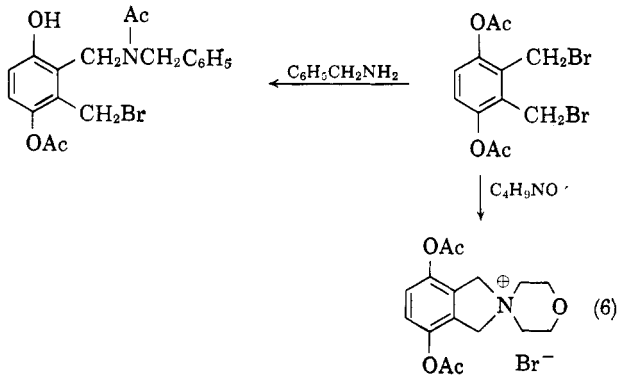


(5)

(1) F. Bell, *J. Chem. Soc.*, 2966 (1931); G. Fodor and K. Nador, *ibid.*, 721 (1953); I. Levi, *Can. J. Chem.*, **39**, 2491 (1961); B. F. Stimmel and C. G. King, *J. Am. Chem. Soc.*, **56**, 1724 (1934); E. E. van Tamelen, *ibid.*, **73**, 5773 (1951); R. B. Martin and Alice Parcell, *ibid.*, **83**, 4835 (1961); A. B. Foster and M. Stacey, *Advan. Carbohydrate Chem.*, **7**, 247 (1952); J. M. Sugihara, *ibid.*, **8**, 1 (1953).

(2) L. W. C. Miles and L. N. Owen, *J. Chem. Soc.*, 817 (1952).

(3) R. Seifert, *J. prakt. Chem.*, [2] **31**, 462 (1885).



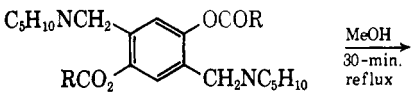
The second type of related reaction is methanolysis of *o*-dialkylaminomethylphenyl esters. In this case the conversion of VI (Z = NR_2^+) to VII yields an acetylating agent similar to the acylammonium ion, $C_5H_5NAc^+$, obtained from pyridine and acetyl chloride. Thus, as shown in Table I, we obtain rapid ester interchange on refluxing in methanol. Again, as required by intermediate VI and as shown in Table II, deacetylation occurs specifically with the ester *ortho* to the dialkylaminomethyl group. Table III shows the expected decrease in rate with decreasing basicity (X *vs.* XV)[4] and with increasing steric hindrance (X *vs.* XVI).

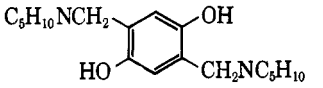
The third type of related reaction is the acetolysis of a dialkylaminomethylphenyl acetate to yield an acetoxymethylphenyl acetate.[5] The similarities between methanolysis and acetolysis in terms of the effect on rate of the basicity of the amine, steric requirements, and enhanced reactivity of an *ortho* group are shown in Table III and suggest that VI is again an intermediate. We assume that in excess acetic anhydride the equilibria shown in Scheme I will prevail and that most of the amine will be in the form of XVIII. Although XVIII can give rise to product by direct nucleophilic displacement (see Table III, compound XIV, for example), the formation of XVIII serves to slow the reaction since it inhibits the formation of VI which is the preferred intermediate for fast acetolysis, as is shown by comparing compounds XIII and XIV, Table III. This preference has been clearly demonstrated[6] in a case where competition between straight displacement and VI is possible (eq. 7). It is interesting to note that this mechanism requires the acyl portion of the amide to come from the acetic anhydride when derived from XVIII and from the ester when derived from VI. We have not yet confirmed this experimentally.

The rate of complete acetolysis of XVII compared

TABLE I

METHANOLYSIS OF PIPERIDINO DERIVATIVES





Compd.	R	Yield, %
X	CH_3	97
XI	$CH_3(CH_2)_3$	100
XII	C_6H_5	90

TABLE II

METHANOLYSIS OF MORPHOLINO DERIVATIVES

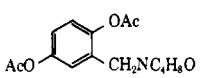
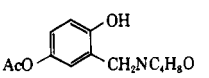
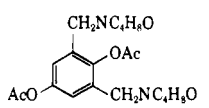
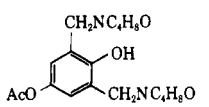
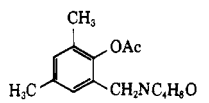
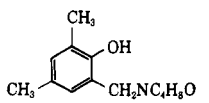
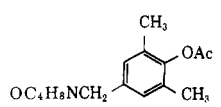
Reactant	Product	Time, hr.	Yield, %
		0.5	51
		0.5	50
 XIII		5	100
 XIV	No Reaction	5	0

TABLE III

EFFECTS OF BASICITY, STERIC HINDRANCE, AND STRUCTURE ON METHANOLYSIS AND ACETOLYSIS

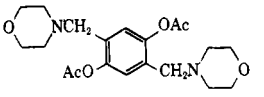
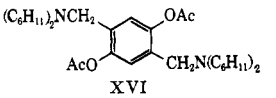
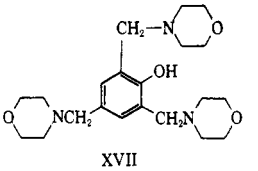
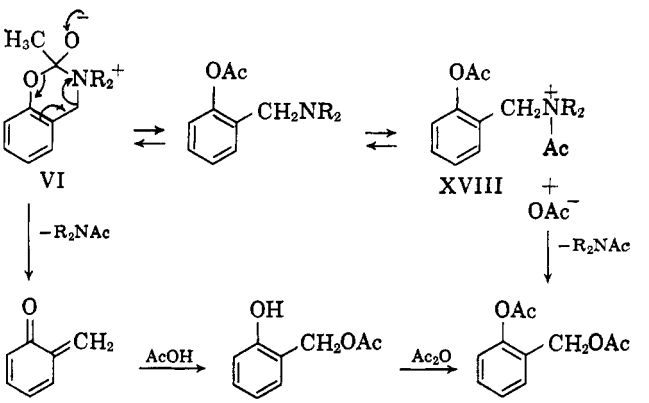
Compd.	Yield, % (hr.) Methanolysis	Yield, % (hr.) Acetolysis
X	97 (0.5)	100 (2)
 XV	81 (0.75) 100 (4)	9 (2)
 XVI	54 (0.5) 93 (5)	0 (2)
XIII	100 (5)	97 (64)
XIV	0 (5)	25 (64) 40 (118)
 XVII		90 (16)

TABLE III

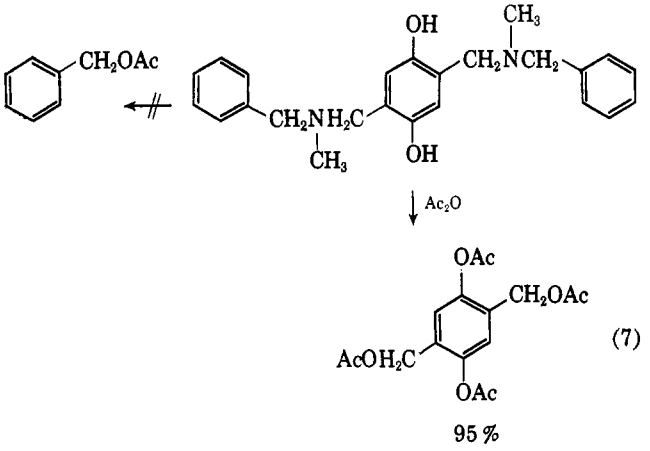
SCHEME I



(4) The pK_b values for morpholine and piperidine are 5.30 and 2.72, respectively: R. J. Bruehlman and F. H. Verhoek, *J. Am. Chem. Soc.*, **70**, 1401 (1948).

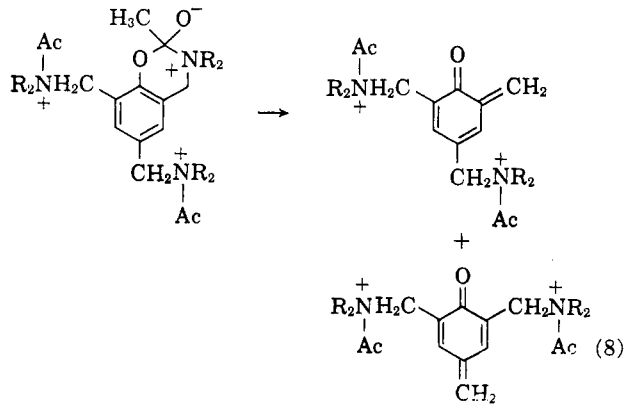
(5) H. A. Bruson and C. W. MacMullen, *ibid.*, **63**, 270 (1941).

(6) D. L. Fields, J. B. Miller, and D. D. Reynolds, *J. Org. Chem.*, **27**, 2749 (1962).



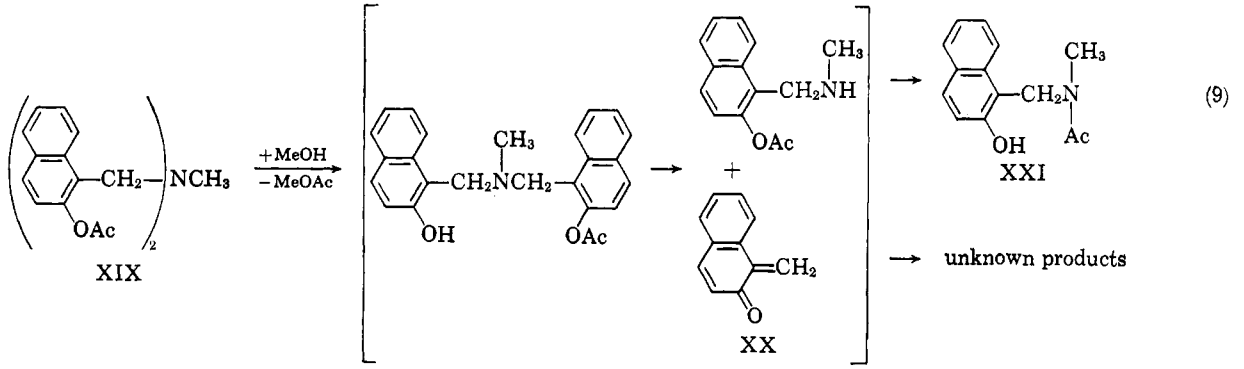
(7)

with that of XIV (Table III) shows that a reaction path for the rapid acetolysis of the *p*-dialkylaminomethyl group is available to the former which is not available to the latter. In the case of XVII the acetic anhydride plays a favorable role in acylating the *p*-amino group. This provides a leaving group, as shown in eq. 8, without



(8)

simultaneously preventing the formation of the cyclic intermediate. The intermediate can then "collapse" to yield either an *ortho*- or a *para*-quinone methide. The *para* isomer will be converted to 2,4,6-tris(acetoxymethyl)phenyl acetate, as indicated in Scheme I. The *ortho* isomer will undergo a similar sequence of reactions, thus providing a second opportunity for facile *para* displacement.



(9)

A reaction having the features of methanolysis, acetolysis (C–N bond cleavage), and rearrangement was observed on refluxing XIX in methanol. Based on eq. 9, an 82% yield of XXI was obtained. Acetylation of XXI gave the N,O-diacetate XXII which was stable to refluxing methanol and is therefore not an intermediate in the conversion of XIX to XXI. The facile cleavage of XIX (as the free phenol) with amines has been described[7] and XX has been proposed as an intermediate.[6] The other product from our reaction is a yellow oil, presumably derived from XX, which has resisted characterization. In particular, attempts to isolate the known dimer of XX[8] have been unsuccessful.

Experimental

2,5-Bis(N-acetyl-N-benzylaminomethyl)hydroquinone (II).—To a solution of 11.4 g. (0.03 mole) of I[9] in 150 ml. of dimethylformamide was added slowly, with stirring, 14 g. (0.13 mole) of benzylamine. After the initial exothermic reaction, the mixture was cooled to room temperature and poured into 2 l. of cold water. The collected solid (13.5 g.) was slurried with hot ethanol to yield 8 g. of product. Crystallization from 50 ml. of hot dimethylformamide gave an analytical sample, m.p. 267–268° dec., with infrared absorption at ν 3150 (—OH) and 1625 cm.$^{-1}$ (amide C=O).

Anal. Calcd. for $C_{26}H_{28}N_2O_4$: C, 72.3; H, 6.5; N, 6.5. Found: C, 72.1; H, 6.6; N, 6.8.

2,5-Bis(acetylthiomethyl)hydroquinone (III).—A solution of 77.4 g. (0.6 mole) of diisopropylethylamine in 1 l. of methanol was saturated with hydrogen sulfide. To this stirred solution was added 110 g. (0.29 mole) of I[9] in small portions. Hydrogen sulfide was bubbled through the solution during the addition which required about 10 min. The solvent was removed under reduced pressure and the resulting solid was washed thoroughly with water. The wet solid was recrystallized from methanol to give two crops: 40.3 g., m.p. 190–193.5°; 7.8 g., m.p. 180–192° (total yield, 58%). Additional recrystallization from methanol gave an analytical sample: m.p. 190–193°, $\nu_{C=O}$ 1640 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{14}O_4S_2$: C, 50.3; H, 5.1; S, 22.4. Found: C, 50.2; H, 5.0; S, 22.2.

2,5-Bis(trifluoroacetoxymethyl)hydroquinone Diacetate (IV).—To a solution of 38 g. (0.1 mole) of I[9] in 500 ml. of methylene chloride was added a solution of 46.4 g. (0.21 mole) of silver trifluoroacetate in 200 ml. of ether. The mixture was stirred overnight and then filtered. Removal of the solvent under reduced pressure gave a solid, which was washed free of color with ether to yield 20.6 g. (46%) of product, m.p. 103–107.5°. Recrystallization from ligroin (b.p. 66–75°) gave an analytical sample: m.p. 107–108.5°, $\nu_{C=O}$ 1750 (acetate) and 1780 cm.$^{-1}$ (trifluoroacetate).

Anal. Calcd. for $C_{16}H_{12}F_6O_8$: C, 43.1; H, 2.7; F, 25.6. Found: C, 43.4; H, 3.1; F, 25.9.

2,5-Bis(acetoxymethyl)hydroquinone (V).—A solution of 10 g. of IV in 1 l. of methanol stood at room temperature for 64 hr. Removal of the solvent under reduced pressure gave 2.0 g. of solid. Recrystallization from methanol gave a sample having the correct analysis and m.p. 165–167° dec. (lit.[10] m.p. 164.5–165°), $\nu_{C=O}$ 1710 cm.$^{-1}$.

(7) W. J. Burke, M. J. Kolbezen, and C. W. Stephens, *J. Am. Chem. Soc.*, **74**, 3601 (1952).

(8) S. B. Cavitt, H. Sarrafizadeh R., and P. D. Gardner, *J. Org. Chem.*, **27**, 1211 (1962).

(9) D. L. Fields, J. B. Miller, and D. D. Reynolds, *ibid.*, **29**, 2640 (1964).

(10) H. v. Euler, E. Adler, H. Hasselquist, and M. Lundin, *Arkiv Kemi, Mineral., Geol.*, **18A**, 23 pp., no. 7 (1944); *Chem. Abstr.*, **39**, 3786^7 (1945).

4-Acetoxy-2-(N-acetyl-N-benzylaminomethyl)phenol (VIII).—A mixture of 10.7 g. (0.1 mole) of benzylamine, 12.6 g. (0.1 mole) of diisopropylethylamine, and 50 ml. of dioxane was added to a solution of 28.7 g. (0.1 mole) of bromomethylhydroquinone diacetate[9] in 200 ml. of dioxane. After 10 min., the solvent was removed, to yield a sirup which was triturated with 400 ml. of cold water. The water was decanted and the sirup was then crystallized by trituration with 150 ml. of ethanol, followed by dilution with 400 ml. of water. Recrystallization from acetone–water gave 22 g. (70%) of pure material: m.p. 144°; ν_{OH} 3150, $\nu_{C=O}$ 1775 (ester) and 1630 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 69.0; H, 6.1; N, 4.5. Found: C, 69.0; H, 6.2; N, 4.8.

3-Benzyl-6-benzyloxy-3,4-dihydro-2H-1-oxa-3-azanaphthalene.—A mixture of 107 g. (1.0 mole) of benzylamine, 60 g. (2.0 moles) of paraformaldehyde, and 400 ml. of ethanol was allowed to react. When the initial exothermic reaction subsided and the mixture was nearly homogeneous, 200 g. (1.0 mole) of 4-benzyloxyphenol was added. The mixture was refluxed for 45 min. and then concentrated to a sirup on the steam bath. Dissolving the sirup in benzene and evaporating it three times gave a sirup which crystallized on trituration with petroleum ether (b.p. 30–60°). An analytical sample was obtained by recrystallization from benzene–petroleum ether (b.p. 30–60°): m.p. 81–84°, 163 g. (49% yield).

Anal. Calcd. for $C_{22}H_{21}NO_2$: C, 79.8; H, 6.4; N, 4.2. Found: C, 80.1; H, 6.5; N, 4.2.

2-(N-Acetyl-N-benzylaminomethyl)-4-benzyloxyphenyl Acetate.—A mixture of 16.8 g. of 3-benzyl-6-benzyloxy-3,4-dihydro-2H-1-oxa-3-azanaphthalene, 200 ml. of ethanol, 200 ml. of water, and 30 ml. of hydrochloric acid was distilled until 200 ml. of distillate had been collected. Cooling the reaction mixture to room temperature and diluting it with an equal volume of water gave 17.3 g. of dried solid. This solid was stirred with 50 ml. of acetic anhydride and 10 ml. of pyridine for 3 hr. The addition of 700 ml. of water gave an oil. The mixture was made slightly basic with sodium bicarbonate and extracted with 550 ml. of chloroform. The chloroform extract was washed with two 100-ml. portions of 5% hydrochloric acid, two 100-ml. portions of water, and two 100-ml. portions of 5% sodium bicarbonate solution. After the chloroform solution had been dried, the solvent was removed under reduced pressure to yield an oil. The oil was dissolved in benzene and the solvent removed to yield an oil which crystallized on standing: 16.3 g., m.p. 74°. Three recrystallizations from ether–petroleum ether gave an analytical sample, m.p. 82.5–86°.

Anal. Calcd. for $C_{25}H_{25}NO_4$: C, 74.5; H, 6.2; N, 3.5. Found: C, 74.3; H, 6.4; N, 3.8.

4-Acetoxy-3-(N-acetyl-N-benzylaminomethyl)phenol (IX).—A mixture of 8.2 g. (0.02 mole) of 2-(N-acetyl-N-benzylaminomethyl)-4-benzyloxyphenyl acetate, 5 g. of 10% palladium on charcoal, and 200 ml. of ethanol was hydrogenated at 63.5 p.s.i. Hydrogenolysis was complete in 30 min. Filtration and removal of the solvent yielded an oil which crystallized on seeding with VIII. Crystallization from ethanol–petroleum ether gave 3.8 g. (60% yield) of product, m.p. 144.5–146°, m.m.p. (with VIII) 118–135°. Recrystallization from the same solvent pair gave 2.9 g. of pure material: m.p. 145–147°, ν_{OH} 3075 cm.$^{-1}$, $\nu_{C=O}$ 1750 (ester) and 1625 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 69.0; H, 6.1; N, 4.5. Found: C, 69.5; H, 6.1; N, 4.4.

4,7-Diacetoxyisoindoline-2-spiro-4′-morpholinium Perchlorate.—Dropwise addition of 17.4 g. (0.2 mole) of morpholine to a solution of 38.0 g. (0.1 mole) of 2,3-bis(bromomethyl)hydroquinone diacetate[9] in 250 ml. of chloroform caused a salt to separate. After 5 min. the solvent was evaporated and the residue was slurried with 100 ml. of water. The insoluble residue (6.4 g., 17% recovery) was identified as the starting material. The aqueous phase was treated with a saturated sodium perchlorate solution which precipitated the quaternary perchlorate. Recrystallization from boiling water gave 20.0 g. (49% conversion, 59% yield) of pure material, m.p. 215–219°.

Anal. Calcd. for $C_{16}H_{20}ClNO_9$: C, 47.3; H, 4.9; N, 3.5; Cl, 8.8. Found: C, 46.9; H, 5.0; N, 3.8; Cl, 8.7.

4-Acetoxy-2-(N-acetyl-N-benzylaminomethyl)-3-bromomethylphenol.— To a mixture of 19.0 g. (0.05 mole) of 2,3-bis(bromomethyl)hydroquinone diacetate,[9] 12.6 g. (0.1 mole) of diisopropylethylamine, and 300 ml. of methylene chloride was added a solution of 5.35 g. (0.05 mole) of benzylamine in 50 ml. of methylene chloride. Addition required 10 min., after which the mixture stood at room temperature for 1 hr. Evaporation gave a crystalline solid which was slurried with 100 ml. of ethanol and then diluted with 1 l. of water. Filtration and recrystallization from acetone–water gave 17.0 g. (84% yield) of pure product: m.p. 194–194.5°, ν_{OH} 3100 cm.$^{-1}$, $\nu_{C=O}$ 1760 (ester) and 1610 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_{17}H_{20}BrNO_4$: C, 56.2; H, 4.9; Br, 19.7; N, 3.6. Found: C, 56.4; H, 5.1; Br, 19.5; N, 4.0.

1-[6-Acetoxy-2-(N-acetyl-N-benzylaminomethyl)-3-hydroxybenzyl]pyridinium Perchlorate.—A mixture of 0.5 g. of 4-acetoxy-2-(N-acetyl-N-benzylaminomethyl)-3-bromomethylphenol and 4 g. of pyridine was allowed to stand at room temperature for 10 min. The addition of ether precipitated the salt which was collected and dissolved in water. Addition of a saturated solution of sodium perchlorate precipitated the product, m.p. 197–199°.

Anal. Calcd. for $C_{24}H_{25}ClN_2O_8$: C, 57.1; H, 5.0; N, 5.6. Found: C, 57.1; H, 5.0; N, 5.6.

2,5-Bis(piperidinomethyl)hydroquinone.—To a suspension of 60 g. (2 moles) of paraformaldehyde in 500 ml. of stirred benzene was cautiously added 170 g. (2 moles) of piperidine. A mildly exothermic reaction ensued, during which time the paraformaldehyde went into solution. One mole (110 g.) of hydroquinone was added and the mixture was refluxed for 2 hr. The solution was concentrated to two-thirds of its volume and refrigerated overnight. The crystalline product was separated and recrystallized from 3 l. of ethyl acetate to yield 224 g. (72.3%) of white needles, m.p. 188–189°.

Anal. Calcd. for $C_{18}H_{28}N_2O_2$: C, 71.0; H, 9.2; N, 9.2. Found: C, 71.2; H, 8.9; N, 9.1.

2,5-Bis(piperidinomethyl)hydroquinone diacetate (X) was prepared from the Mannich base and acetic anhydride, m.p. 135–137° [from benzene–ligroin (b.p. 30–60°)].

Anal. Calcd. for $C_{22}H_{32}N_2O_4$: C, 68.1; H, 8.3; N, 7.2. Found: C, 67.7; H, 8.2; N, 7.2.

2,5-Bis(piperidinomethyl)hydroquinone divalerate (XI) was prepared from the Mannich base and valeric anhydride, m.p. 73–75° (from ligroin).

Anal. Calcd. for $C_{28}H_{44}N_2O_4$: C, 71.2; H, 9.3; N, 5.9. Found: C, 70.7; H, 9.4; N, 6.0.

2,5-Bis(piperidinomethyl)hydroquinone dibenzoate (XII) was prepared from the Mannich base and benzoyl chloride in dioxane–chloroform, m.p. 169–171.5° (from benzene).

Anal. Calcd. for $C_{32}H_{36}N_2O_4$: C, 75.0; H, 7.0; N, 5.5. Found: C, 75.0; H, 7.2; N, 5.8.

Morpholinomethylhydroquinone diacetate was prepared from the Mannich base[9] and acetic anhydride, m.p. 81.5–84.5° (from benzene–petroleum ether).

Anal. Calcd. for $C_{15}H_{19}NO_5$: C, 61.4; H, 6.5; N, 4.8. Found: C, 61.5; H, 6.3; N, 4.6.

2,4-Dimethyl-6-morpholinomethylphenyl Acetate (XIII).—A mixture of 61 g. (0.5 mole) of 2,4-dimethylphenol, 87 g. (0.6 mole) of ethoxymethylmorpholine,[11] and 100 ml. of ethanol was refluxed overnight. Removal of the solvent and distillation gave 96.5 g. (88% yield) of the Mannich base, b.p. 127–130° (0.5–0.6 mm.), $n^{25}D$ 1.5337.

The product was stirred for 2 hr. with 140 ml. of acetic anhydride and then poured into water. The resulting homogeneous solution was neutralized with sodium bicarbonate, which precipitated 70.9 g. (62% yield) of product, m.p. 78–79.5°. Recrystallization from petroleum ether gave an analytical sample, m.p. 78.5–81°.

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.5; H, 7.9; N, 5.3. Found: C, 68.1; H, 8.1; N, 5.3.

2,6-Dimethyl-4-morpholinomethylphenyl Acetate (XIV).—A mixture of 122 g. (1.0 mole) of 2,6-dimethylphenol, 174 g. (1.1 moles) of ethoxymethylmorpholine,[11] and 200 ml. of ethanol was refluxed for 12 hr. The solvent was removed and 250 g. (2.4 moles) of acetic anhydride was added. After the mixture had been stirred for 1 hr., the volume was reduced by one-half under reduced pressure and the residual solution was poured into water. The solution was neutralized with sodium bicarbonate and extracted with chloroform. The chloroform extract was washed with water and dried with magnesium sulfate. Removal of the solvent, followed by distillation, gave an analytical sample, b.p. 121° (0.06 mm.), $n^{25}D$ 1.5171.

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.5; H, 7.9; N, 5.3. Found: C, 68.1; H, 7.8; N, 5.0.

(11) J. P. Mason and M. Zief, *J. Am. Chem. Soc.*, **62**, 1450 (1940).

2,5-Bis(morpholinomethyl)hydroquinone diacetate (XV) was prepared from the Mannich base[9] and acetic anhydride, m.p. 178–181.5° (from acetic acid).

Anal. Calcd. for $C_{20}H_{28}N_2O_6$: C, 61.2; H, 7.1; N, 7.1. Found: C, 61.6; H, 7.1; N, 7.1.

2,5-Bis(dicyclohexylaminomethyl)hydroquinone Diacetate (XVI).—A mixture of 51.6 g. (0.136 mole) of 2,5-bis(bromomethyl)hydroquinone diacetate,[9] 49.2 g. (0.272 mole) of dicyclohexylamine, 35 g. (0.272 mole) of diisopropylethylamine, 1 l. of methylene chloride, and 500 ml. of dioxane was refluxed for 17 hr. The mixture was filtered and the crystalline residue (30 g., 53% yield) of diisopropylethylammonium bromide was washed with methylene chloride. The filtrate was washed with three 500-ml. portions of water and dried with sodium sulfate. Removal of the solvent under reduced pressure gave a pasty solid which was washed with petroleum ether to yield 53.2 g. of a solid, m.p. 120–200°, positive Beilstein halogen test. The solid was mixed with 200 ml. of pyridine and, after 30 min., 400 ml. of water was added to it. The mixture was filtered and the solid residue was washed with water until free of pyridine to yield 29.4 g. (37% yield) of product, m.p. 193–199°. An analytical sample was prepared by recrystallization from cyclohexane, m.p. 198.5–203°.

Anal. Calcd. for $C_{36}H_{56}N_2O_4$: C, 74.5; H, 9.6; N, 5.0. Found: C, 73.9; H, 9.6; N, 5.0.

Methanolysis of X–XV.—Five grams of the ester was refluxed in 50 ml. of methanol for the stated time (see Tables I, II, and III). In the case of XV and XVI, 50 and 75 ml. of chloroform, respectively, was added. After evaporation of the solvent, the product, if pure, was characterized by its infrared spectrum and its melting point or refractive index. If not pure, the product was recrystallized before characterization.

4-Acetoxy-2-morpholinomethylphenol.—After a solution of 5 g. of morpholinomethylhydroquinone diacetate in 50 ml. of methanol had been refluxed for 30 min., the solvent was removed under reduced pressure. The resulting sirup crystallized on scratching to give 3.2 g. (72% yield) of crude product, m.p. 57–62°. Two recrystallizations from benzene–petroleum ether gave an analytical sample, m.p. 61–63°.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.2; H, 6.8; N, 5.6; Ac, 17.1. Found: C, 62.5; H, 7.1; N, 5.5; Ac, 17.7.

2,6-Bis(morpholinomethyl)hydroquinone Diacetate.—After standing overnight, a mixture of 30.8 g. (0.10 mole) of 2,6-bis(morpholinomethyl)hydroquinone[12] and 100 ml. of acetic anhydride was diluted with water. When hydrolysis was complete, the solution was neutralized with solid sodium bicarbonate. The resulting solid was collected and washed with water to yield 24 g. of product, m.p. 115–118°. The filtrate was saved and used in the next preparation. Two recrystallizations from benzene–petroleum ether gave an analytical sample, m.p. 120–122°.

Anal. Calcd. for $C_{20}H_{28}N_2O_6$: C, 61.2; H, 7.2; N, 7.2; Ac, 21.9. Found: C, 61.1; H, 7.4; N, 7.0; Ac, 22.3.

4-Acetoxy-2,6-bis(morpholinomethyl)phenol. A. By Acetylation.—The preceding filtrate was made basic to litmus with solid sodium bicarbonate. The solid which precipitated was collected, washed, and dried to yield 9 g. of the title compound, m.p. 128°. Two recrystallizations from benzene–petroleum ether gave an analytical sample, m.p. 132–133°.

Anal. Calcd. for $C_{18}H_{26}N_2O_5$: C, 61.8; H, 7.5; N, 8.0; Ac, 12.3. Found: C, 62.1; H, 7.7; N, 8.0; Ac, 12.5.

B. By Methanolysis.—A solution of 5 g. of 2,6-bis(morpholinomethyl)hydroquinone diacetate in 50 ml. of methanol was refluxed for 30 min. Evaporation of the solvent gave a sirup which was crystallized from benzene–petroleum ether to yield 2.2 g. (50%) of product, m.p. 126.5–129°. Two recrystallizations from ethanol gave material identical with that prepared in A above, m.p. 130–131.5°.

2,5-Bis(dicyclohexylaminomethyl)hydroquinone.—A solution of 5.0 g. of XVI in 75 ml. of chloroform and 50 ml. of methanol was refluxed for 5 hr. Filtration gave 4.0 g. (93% yield) of carbonyl-free product, m.p. 250° dec. No suitable solvent could be found for recrystallization of the free base. Two recrystallizations from 5% hydrochloric acid gave an analytical sample of the **dihydrochloride**, m.p. 179–185° dec.

Anal. Calcd. for $C_{32}H_{54}Cl_2N_2O_2$: C, 67.6; H, 9.5; Cl, 12.5; N, 4.9. Found: C, 67.8; H, 9.6; Cl, 12.1; N, 4.9.

Acetolysis of X, XV, and XVI.—A solution of 5 g. of the acetate (or free hydroquinone) in 50 ml. of acetic anhydride was refluxed for the designated time (see Table III). Removal of the solvent under reduced pressure and dilution with water gave 2,5-bis(hydroxymethyl)hydroquinone tetraacetate.[7]

Acetolysis of XIII and XIV.—A solution of 21.7 g. of the acetate in 200 ml. of acetic anhydride was refluxed for the designated time (see Table III). The solvent was removed under reduced pressure and the residual liquid was diluted with water. The mixture was extracted with 100 ml. of chloroform and the chloroform extract was washed with 100 ml. of 5% hydrochloric acid and two 100-ml. portions of water. After the extract had been dried with sodium sulfate and the solvent had been removed, the residual oil was distilled.

Compound XIII gave **2-acetoxymethyl-4,6-dimethylphenyl acetate**: b.p. 100° (0.075 mm.), $n^{25}D$ 1.4979, retention time[13] 1.69.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.1; H, 6.8. Found: C, 66.4; H, 7.1.

Compound XIV gave **4-acetoxymethyl-2,6-dimethylphenyl acetate**: b.p. 110–114° (0.25 mm.), $n^{25}D$ 1.4991, retention time 2.01.[13]

Anal. Found: C, 66.2; H, 7.1.

Acetolysis of XVII.—A solution of 78.2 g. (0.2 mole) of XVII in 500 ml. of acetic anhydride was refluxed for 16 hr. Removal of the solvent and dilution with water gave an oil. The mixture was acidified to pH 2 with concentrated hydrochloric acid and extracted with three 100-ml. portions of benzene. The benzene extracts were washed with water and 5% sodium bicarbonate. After the extracts had been dried and the solvent removed, there was obtained 58 g. (90% yield) of **2,4,6-tris(acetoxymethyl)phenyl acetate**, $n^{25}D$ 1.4995. The infrared spectrum was identical with that of an authentic sample prepared by the method of Bruson and MacMullen[5]: b.p. 175–177° (0.05 mm.), $n^{25}D$ 1.4993.

Anal. Calcd. for $C_{17}H_{20}O_8$: C, 58.0; H, 5.7. Found: C, 58.1; H, 6.0.

Methanolysis of N,N-Bis(2-acetoxy-1-naphthylmethyl)methylamine (XIX).—A solution of 42.7 g. of XIX[7] in 500 ml. of methanol was refluxed for 18.5 hr. The solution was cooled and filtered to yield 16 g. of XXI, m.p. 196–197.5° (lit.[6] m.p. 199–200°). Removal of the solvent from the filtrate gave a mixture of yellow oil and crystals. The addition of 100 ml. of ether and filtration gave an additional 2.8 g. of XXI, m.p. 193–196° (total yield, 82%). On evaporation, the ether filtrate gave a yellow oil which resisted characterization.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.4; H, 6.6; N, 6.1. Found: C, 73.3; H, 6.7; N, 5.6.

Acetylation of XXI with acetic anhydride gave XXII, m.p. 122° (lit.[7] m.p. 123–125°). This compound was recovered unchanged after the solution had been refluxed for 16 hr. in methanol.

Acknowledgment.—We gratefully acknowledge the assistance of Dr. O. E. Schupp, Miss Jane Fournier, and Mr. J. W. Westman, all of Kodak Research Laboratories.

(12) W. J. Burke, J. A. Warburton, J. L. Bishop, and J. L. Bills, *J. Org. Chem.*, **26**, 4669 (1961).

(13) Relative to dimethyl phthalate on a column of silicone oil 200 on acid- and base-washed Celite 545 at 229°.