We wish to thank Mr. W. L. Brown, Mrs. Shirley Caper and Mr. H. L. Hunter for the microanalyses reported in this paper.

Summary

A number of cyclic secondary amines, pyrrole, pyrrolidine, piperidine, the three monomethylpiperidines, three dimethylpiperidines, 1,2,3,4-tetrahydroquinoline, and imidazole have been used to prepare side chains for 2-methoxy-6-chloro-9-(N-substituted amino)-acridines related to quinacrine.

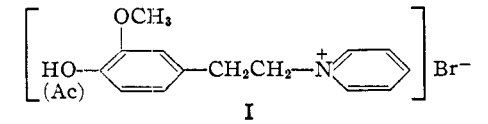
INDIANAPOLIS, INDIANA RECEIVED APRIL 25, 1946

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

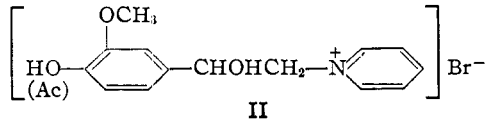
Pyridinium Analogs of the Pressor Amines. II. The Guaiacol Series[1]

BY BYRON RIEGEL AND HAROLD WITTCOFF[2]

The desire for more complete physiological data for correlative purposes prompted the preparation of a series of pyridinium analogs of the pressor amines similar to those described in the preceding paper[3] save that the aromatic nuclei were substituted so as to relate them to guaiacol. Formulas I–IV indicate the products synthesized; compounds I, II and IV having been obtained not as the free phenols, but as the acetates.



I



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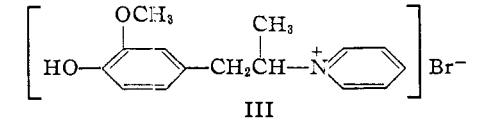
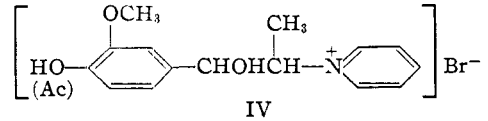


III



IV

β - (3 - Methoxy - 4 - acetoxyphenyl) - ethylpyridinium bromide (I) resulted from the interaction of anhydrous pyridine with β-(3-methoxy-4-acetoxyphenyl)-ethyl bromide in dry benzene. The bromide, whose structure was deduced indirectly, was obtained by the non-Markownikoff addition of hydrogen bromide to 4-vinylguaiacol acetate according to the conditions which previously had effected a similar reaction with styrene.[4] 4-Vinylguaiacol acetate resulted from the decarboxylation of acetylferulic acid according to the procedure outlined by Reichstein[5] for the preparation of 4-vinylguaiacol. Evidence for reverse hydrobromination derived from the fact that formation of the pyridinium salt required steam-bath temperatures. If the bromide were of secondary nature, the pyridinium salt would have formed only with great difficulty as examples in this and the preceding paper indicate. Indeed, it is known that secondary halides in which the halogen is adjacent to a phenyl nucleus are unstable oils which undergo dehydrohalogenation readily with pyridine to yield the parent vinyl compound.[6] Our attempts to prepare β-(3-methoxy-4-hydroxyphenyl)-ethyl bromide are described in the experimental part.

β - (3 - Methoxy - 4 - acetoxyphenyl) - β - hydroxyethylpyridinium bromide (II) was formed by the high pressure catalytic reduction of 3-methoxy-4-acetoxyphenacylpyridinium bromide. Although the procedure was similar to that used for the successful reduction of phenacylpyridinium bromide,[3] the yield was vitiated by the formation of a by-product, the piperidinium salt of 4-bromoacetylguaiacol acetate which was identified by comparison with an authentic sample.

A desire to prepare β-(3-methoxy-4-hydroxyphenyl)-β-hydroxyethylpyridinium bromide occasioned the preparation of 3-methoxy-4-hydroxyphenacylpyridinium bromide. This material, however, proved too insoluble to be amenable to catalytic reduction.

4-Bromoacetylguaiacol, necessary for the preparation of 3-methoxy-4-acetoxyphenacylpyridinium bromide, was synthesized in 75% yield by the direct interaction of bromoacetyl bromide and guaiacol in a Friedel–Crafts type of reaction. At low temperatures the reaction proceeded smoothly and was not accompanied with demethylation. The direct haloacylation of guaiacol has not previously been described, although similar compounds have been prepared by the simultaneous acylation and demethylation of veratrole.[7] The structure of the brominated ketone was proved by the reductive removal of the halogen atom according to the method of Pratt and Robinson[7] to obtain 4-acetylguaiacol, identified by its phenylhydrazone.

The preparation of 4-(α-hydroxy-β-bromoethyl)-guaiacol acetate, which on reaction with

(1) From the Ph.D. thesis by Harold Wittcoff, June, 1943.

(2) Present address: General Mills, Inc., Minneapolis, Minn.

(3) B. Riegel and H. Wittcoff, THIS JOURNAL, **68**, 1805 (1946).

(4) C. Walling, M. S. Kharasch and F. R. Mayo, *ibid.*, **61**, 2693 (1939).

(5) T. Reichstein, *Helv. Chim. Acta*, **15**, 1450 (1932).

(6) R. Quelet, *Compt. rend.*, **202**, 956 (1936).

(7) D. D. Pratt and R. Robinson, *J. Chem. Soc.*, **123**, 745 (1923).

pyridine should likewise yield II, was attempted by various procedures. The interaction of hypobromous acid with 4-vinylguaiacol acetate under varied conditions yielded either indefinite tarry products or starting material. Nor could the preferential hydrolysis of the α-bromine atom of 4-(α,β-dibromoethyl)-guaiacol acetate according to well-known procedures[8,9] be accomplished successfully. Still another attempted preparation of the bromohydrin involved the aluminum isopropoxide catalyzed reduction of 4-bromoacetylguaiacol acetate according to the procedure which is feasible for phenacyl bromide.[10] Although acetone was readily detectable, there resulted only an intractable tar. The phenolic character of the molecule probably contributes to these unfavorable results.

From the interaction of pyridine with 4-(β-bromopropyl)-guaiacol, the normal hydrobromination product of eugenol, resulted the β-(3-methoxy - 4 - hydroxyphenyl) - isopropylpyridinium bromide (III). The tendency for dehydrohalogenation which is characteristic of secondary halides interfered somewhat with the yields.

β - (3 - Methoxy - 4 - acetoxyphenyl) - β - hydroxyisopropylpyridinium bromide (IV) was obtained in 75% yield from the catalytic reduction of the corresponding ketone. Here, as with the unsubstituted compound,[3] a lower melting form was not isolated, although an uncrystallizable oil was observed. That the compound obtained was not the piperidinium salt of 4-(α-bromopropionyl)-guaiacol acetate was indicated by the strong depression obtained on mixed melting point with an authentic sample of the piperidinium derivative. The postulation that the reduction product might be β-(3-methoxy-4-acetoxyphenyl) - β - hydroxyisopropylpiperidinium bromide was obviated by the fact that the absorption of only one mole of hydrogen would render impossible the formation of this compound in 75% yield. The formation of a hydroxyl group was indicated by acetylation to obtain a diacetate.

The attempted reduction, on the other hand, of 3-methoxy-4-hydroxypropiophenonylpyridinium bromide yielded an oily mixture presumably of all the possible reduction products.

For the preparation of the intermediate pyridinium ketone subjected to catalytic reduction, it was necessary to synthesize 4-(α-bromopropionyl)-guaiacol, a compound which previously had been prepared by Cramer and Hibbert[11] by the simultaneous demethylation and acylation of veratrole. Here again it was found possible to effect the direct α-haloacylation of guaiacol without demethylation. Furthermore, the difficulty encountered by the previous investigators in crystallizing the product was eliminated when the direct procedure was employed. However, since the melting point of 102–103° observed in this Laboratory was several degrees lower than that indicated by the Canadian investigators, and since the structure of their compound was established by analogy, it was decided to synthesize the acetate of the compound by an alternative procedure in order to establish unequivocally its structure. The acetylation and subsequent bromination of 4-propionylguaiacol[12] yielded 4-(α-bromopropionyl)-guaiacol acetate. A mixed melting point with the material resulting from the acetylation of the condensation product of α-bromopropionyl bromide with guaiacol was not depressed.

Various attempts were made to prepare 4-(α-hydroxy - β - bromopropyl)-guaiacol, the bromohydrin which on reaction with pyridine would yield IV. Similarly, however, to the observations described previously the Meerwein–Ponndorf reduction of 4-(α-bromopropionyl)-guaiacol or its acetate led only to tar formation. Attempted hypobromous acid addition to isoeugenol or its esters yielded only indefinite oily products in accord with the observations of Read and Reid.[13] Auwers and Müller[8] reported the preparation of 4-(α-hydroxy-β-bromopropyl)-guaiacol as a characterizable oil by the preferential hydrolysis of the α-bromine atom of isoeugenol dibromide. A similar reaction on the benzoate of isoeugenol dibromide did not yield the hoped for crystalline product, although the oily material analyzed fairly well for the desired bromohydrin. Reaction with pyridine yielded a negligible amount of solid material.

These compounds are being screened in several pharmacological tests, one of which is their possible inhibitory action on tumor growth.

The authors are indebted to the Smith, Kline and French Laboratories for the financial assistance which made this research possible.

Experimental[14]

4-Vinylguaiacol Acetate.—To an intimate mixture of 30 g. of acetylferulic acid[15] and 6 g. of copper-bronze in a 1-liter, round-bottom flask, equipped with a Hopkins condenser head and a reflux condenser, was added 60 g. of freshly distilled quinoline. The reaction mixture was immersed for fifteen minutes in a metal-bath which previously had been heated to 240°. In one experiment it was noted that about 75% of the theoretically calculated amount of carbon dioxide was evolved. An ether solution of the contents of the cooled flask was filtered and washed successively with dilute acid, dilute carbonate, and water. Concentration of the dried ether solution yielded a black oil which was distilled over a period of six hours at 10^{-5} mm. at a maximum temperature of 80°. A light yellow oil (6 g., 25%) was obtained which absorbed bromine, and which was stabilized with a few crystals of hydroquinone.

Anal. Calcd. for $C_{11}H_{12}O_3$: sapn. equiv., 192.2. Found: sapn. equiv., 184.7.

(8) K. Auwers and O. Müller, *Ber.*, **35**, 114 (1902).
(9) P. Hoering, *ibid.*, **38**, 3464 (1905).
(10) H. Lund, *ibid.*, **70**, 1520 (1937).
(11) A. B. Cramer and H. Hibbert, THIS JOURNAL, **61**, 2204 (1939).
(12) C. E. Coulthard, J. Marshall and F. L. Pyman, *J. Chem. Soc.*, 280 (1930).
(13) J. Read and W. G. Reid, *ibid.*, 1487 (1928).
(14) All melting points are corrected.
(15) L. S. Fosdick and A. C. Starke, Jr., THIS JOURNAL, **62**, 3352 (1940).

β-(3-Methoxy-4-acetoxyphenyl)-ethylpyridinium Bromide (I).—Into a reaction mixture consisting of 4 g. of 4-vinylguaiacol acetate, 460 ml. of pentane, 150 ml. of dry benzene and 1 g. of benzoyl peroxide was bubbled over a period of twenty minutes 4 g. of gaseous hydrogen bromide. A green oil which adhered to the sides of the vessel separated. The solvent was removed at 40° with the aid of a stream of dry air, after which the oil was washed with ether, in which it was insoluble, to remove the benzoyl peroxide.

To an ether suspension of this oil, presumably β-(3-methoxy-4-acetoxyphenyl)-ethyl bromide, was added 15 ml. of dry pyridine. Solution having been effected by the addition of 20 ml. of benzene, the reaction mixture was refluxed on the steam-bath for one hour. The resulting precipitate was extracted with water, whereupon the aqueous solution was treated with Norit, and concentrated to obtain an oil which crystallized readily and was purified by several crystallizations from absolute alcohol. The resulting product (0.5 g.) melted at 214–216°.

Anal. Calcd. for $C_{16}H_{18}BrNO_3$: Br, 22.7. Found: Br, 22.4.

4-Bromoguaiacol Benzyl Ether.—The benzylation of 4-bromoguaiacol was accomplished according to the general procedure of Powell and Adams.[16] Thus refluxing for eight hours 19 g. of 4-bromoguaiacol,[17] 11 g. of benzyl chloride, 12 g. of potassium carbonate, and 15 ml. of acetone produced a product which after several crystallizations from 95% ethanol yielded 20 g. (74%) of white needles which melted sharply at 61.0–61.2°. Distillation was accomplished at 172–176° at 2 mm.

Anal. Calcd. for $C_{14}H_{13}BrO_2$: C, 57.35; H, 4.47. Found: C, 57.75; H, 4.31.

4-Bromoguaiacol benzyl ether was converted to a Grignard reagent which reacted with ethylene oxide to obtain presumably a substituted phenylethyl alcohol. It was then planned to debenzylate and treat the resulting product with phosphorus tribromide. This should have yielded the bromide necessary for the preparation of I. Since the debenzylation proceeded with difficulty, this synthetic route was abandoned.

4-Bromoacetylguaiacol.—To a mechanically stirred solution of 28 g. of bromoacetyl bromide and 90 ml. of freshly distilled carbon disulfide, surrounded by a freezing mixture of ice and calcium chloride, was added 37.3 g. of anhydrous aluminum chloride after which 17.4 g. of guaiacol was added dropwise. The resulting vigorous reaction, accompanied by the evolution of copious quantities of hydrogen halide, was stirred for one hour at the reduced temperature, whereupon stirring was continued at room temperature for six hours. The orange complex, which gradually darkened, was decomposed carefully with ice and dilute hydrochloric acid. The solution which resulted on extraction of the reaction mixture with ether, having been washed well, dried over sodium sulfate, and concentrated *in vacuo*, yielded a readily crystallizable oil. Several crystallizations from petroleum ether or from a mixture of the latter solvent with 95% ethanol yielded short needles (25 g., 75%) which melted at 78–79°.

Anal. Calcd. for $C_9H_9BrO_3$: Br, 32.6. Found: Br, 32.3.

4-Acetylguaiacol.—This product, the formation of which served as proof of structure for 4-bromoacetylguaiacol, was prepared from 4-bromoacetylguaiacol by the reductive removal of the halogen atom according to the procedure employed by Pratt and Robinson[7] on 4-chloroacetylguaiacol. The resulting product of melting point 113–114° yielded a phenylhydrazone which melted at 125° in accord with the constants cited by the previous investigators.

(16) S. G. Powell and R. Adams, THIS JOURNAL, **42**, 646 (1920).

(17) P. W. Robertson, *J. Chem. Soc.*, **93**, 788 (1908). This author used glacial acetic acid and sodium acetate as a medium for bromination. Slightly better yields (82%) resulted from the dropwise addition of a solution of bromine in chloroform to an ice-cold solution of guaiacol in chloroform. The product distilled at 119–120° at 5 mm. and at 131–134° at 24 mm.

4-Bromoacetylguaiacol Acetate.—The acetylation of 4-bromoacetylguaiacol (3 g.) was accomplished at room temperature by an acetylating mixture of 15 ml. of acetic anhydride and 2 drops of concd. sulfuric acid. After one hour, the reaction mixture was cooled in ice and poured with stirring into ice water to obtain a product which on crystallization from absolute ethanol yielded needles (2.5 g., 81%) melting at 92–93°.

Anal. Calcd. for $C_{11}H_{11}BrO_4$: Br, 27.8. Found: Br, 28.2.

3-Methoxy-4-hydroxyphenacylpyridinium Bromide.—A solution of 15 g. of 4-bromoacetylguaiacol in 40 ml. of anhydrous ether was refluxed for one hour with 4 g. of dry pyridine to obtain crystals (16.5 g., 82.5%) which were dissolved in 1 liter of water to obtain a solution which was treated with Norit. Vacuum concentration of the solution to about three-fourths of its original volume caused the precipitation of the product which after several crystallizations from water yielded 7 g. (33%) of needles melting at 252–253°. The insolubility of the product in ordinary solvents precluded its catalytic reduction.

Anal. Calcd. for $C_{14}H_{14}BrNO_3$: Br, 24.6. Found: Br, 24.4.

3-Methoxy-4-acetoxyphenacylpyridinium Bromide.—A procedure similar to that described above was employed to react 15 g. of 4-bromoacetylguaiacol acetate in 100 ml. of dry benzene with 10 ml. of anhydrous pyridine. After one crystallization from absolute alcohol there resulted long needles (13 g., 70%). During a second crystallization from the same solvent, all the material dissolved save a few particles. While crushing these with a glass rod in an attempt to effect their solution, a flocculent precipitate appeared in the boiling solution. In order to cause redissolution three times as much solvent as for the original material was required. The purified product (11 g., 60%) melted at 228–229°. In later experiments only the difficultly soluble form was obtained, whereas the more soluble form was characterized by long needles; the less soluble material was in the form of short needles. Analysis indicated the presence of one-half mole of ethanol.

Anal. Calcd. for $C_{16}H_{16}BrNO_4 \cdot {}^1/_2C_2H_5OH$: Br, 20.5. Found: Br, 20.6.

β-(3-Methoxy-4-acetoxyphenyl)-β-hydroxyethylpyridinium Bromide[18] (II).—A solution of 1 g. of 3-methoxy-4-acetoxyphenacylpyridinium bromide in 9 ml. of water in the presence of 100 mg. of platinum oxide was subjected to a pressure of 320 pounds of hydrogen at room temperature. After 1 mole of hydrogen had been absorbed above that required to reduce the catalyst, the latter was removed by filtration and the solvent was evaporated *in vacuo* to obtain an oil which did not crystallize readily. The oil, dissolved in a large amount of ethanol, gave rise after several weeks in the cold room to about 200 mg. of needles which after further crystallization from absolute ethanol melted at 216–218°, and which depressed the melting point of the starting material.

Anal. Calcd. for $C_{16}H_{18}BrNO_4$: Br, 21.7. Found: Br, 21.5.

From the mother liquor there was obtained by the addition of ether 300 mg. of a product which was quite soluble in absolute ethanol and which, after purification by precipitation from this solvent with ether, melted at 235–237°. This material did not depress the melting point of a sample of 3-methoxy-4-acetoxyphenacylpiperidinium bromide, the preparation of which follows.

3-Methoxy-4-acetoxyphenacylpiperidinium Bromide.—A solution of 1 g. of 4-bromoacetylguaiacol acetate in 5 ml. of dry benzene reacted with 1 ml. of piperidine on the steam-bath for a few moments. The product, crystallized from absolute ethanol, yielded 0.7 g. (77.2%) of white crystals which melted at 236–237°.

Anal. Calcd. for $C_{16}H_{23}BrNO_4$: Br, 21.5. Found: Br, 21.1.

(18) See footnote (10), preceding article. Thanks are also due to Samuel Siegel and George Lanzl for performing certain experiments.

β-(3-Methoxy-4-hydroxyphenyl)-isopropyl Bromide.—Into an ice-cold solution of 50 g. of eugenol in 100 ml. of petroleum ether (b. p. 30–60°) was bubbled a rapid stream of hydrogen bromide for a period of two hours. The product precipitated as a heavy, blue viscous oil. Although the weight of the reaction vessel indicated the absorption of only one-half the calculated amount of hydrogen bromide, longer reaction periods did not lead to more complete absorption. The product was washed with small portions of petroleum ether and the washings were added to the original solvent. To the petroleum ether solution which contained unreacted eugenol was added 50 g. more of the unsaturate and the process of hydrobromination was repeated. The combined products were distilled under diminished pressure to obtain an oil (70 g., 45%) which exhibited a bluish fluorescence. The distillation ranges observed were 170–171° at 13 mm., 152–155° at 5 mm., 150° at 3 mm., and 144–145° at 1 mm.

Anal. Calcd. for $C_{10}H_{13}BrO_2$: Br, 32.6. Found: Br, 33.0.

β-(3-Methoxy-4-hydroxyphenyl)-isopropylpyridinium Bromide (III).—To a solution of 13 g. of β-(3-methoxy-4-hydroxyphenyl)-isopropyl bromide in 10 ml. of anhydrous ether was added 4.2 g. of dry pyridine. The turbid reaction mixture which resulted after fifteen minutes of gentle heating on the steam-bath was allowed to stand in the cold room overnight, whereupon it was diluted with a large excess of ether. The resulting oil solidified readily. The original mother liquor was evaporated *in vacuo* to obtain an oil which was taken up in ether and treated further with pyridine. The continued repetition of this procedure yielded 3.6 g. (30%) of product which after crystallization from absolute ethanol melted at 221–222°.

Anal. Calcd. for $C_{15}H_{18}BrNO_2$: Br, 24.7. Found: Br, 24.9.

4-(α-Bromopropionyl)-guaiacol.—The reaction was effected similarly to the procedure described for 4-bromoacetylguaiacol using 8 g. of α-bromopropionyl chloride, 30 ml. of freshly distilled carbon disulfide, 11 g. of anhydrous aluminum chloride and 5 g. of guaiacol. After the reaction mixture had been stirred for five hours at room temperature, the brown complex was decomposed with ice cold, dilute hydrochloric acid, whereupon the carbon disulfide layer was separated quickly. The crystalline product which resulted almost at once (5 g., 48%) was crystallized from aqueous alcohol to yield 4.5 g. (43%) of white, silky needles which melted at 102–103° (lit.[11] 105–106°).

Anal. Calcd. for $C_{10}H_{11}BrO_3$: Br, 30.8. Found: Br, 30.4.

Other experimental conditions were not encouraging. The use of zinc chloride as condensing agent led to an impure product. The use of a mixture of tetrachloroethane and nitrobenzene as solvent[19] after three days at 0° yielded an uncrystallizable oil.

4-Propionylguaiacol Acetate.—4-Propionylguaiacol[12] was subjected for several hours at room temperature to the acetylating action of 25 ml. of acetic anhydride and a few drops of concd. sulfuric acid. The reaction mixture, cooled in ice and made turbid by the dropwise addition of water, was poured with stirring into 2 liters of ice water. The resulting sirup which solidified readily was crystallized from 95% ethanol to yield a product (6 g., 80%) melting at 76.5°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.48; H, 6.49.

4-(α-Bromopropionyl)-guaiacol Acetate.—**(A)** The bromination of 4-propionylguaiacol acetate was accomplished in either glacial acetic acid or chloroform, the latter solvent producing somewhat higher yields. A solution of 5 g. of the ketone in 25 ml. of chloroform was treated with 3 drops of bromine and allowed to stand until decolorization and the evolution of hydrogen bromide resulted. Thereafter, a solution of 3.6 g. of bromine in 10 ml. of chloroform was added to the ice-cooled solution over a period of one hour with vigorous stirring. After the stirring had been continued for one hour at room temperature, the solvent was removed *in vacuo* to obtain a product which yielded silky needles (5 g., 75%) from 95% ethanol and which melted at 87°.

(B) The acetylation of 0.9 g. of 4-(α-bromopropionyl)-guaiacol was accomplished by the use of 4 ml. of acetic anhydride and 2 drops of concentrated sulfuric acid according to the procedure indicated for the preparation of 4-bromopropionylguaiacol acetate. There resulted 1 g. (96%) of essentially pure material which on crystallization from aqueous ethanol yielded 0.9 g. (86%) of product melting at 87° and indicating no depression of melting point on admixture with the product described under (A).

Anal. Calcd. for $C_{12}H_{13}BrO_4$: Br, 26.5. Found: Br, 26.1.

3-Methoxy-4-hydroxypropiophenonylpyridinium Bromide.—A benzene solution of 10 g. of 4-(α-bromopropionyl)-guaiacol and 4 g. of anhydrous pyridine was refluxed for one hour. The crystalline mass which resulted (9 g., 65%) after several crystallizations from aqueous ethanol melted at 230–231°.

Anal. Calcd. for $C_{15}H_{16}BrNO_3$: Br, 23.6. Found: Br, 23.1.

The attempted catalytic reduction of this product according to previously described procedures yielded a brown oil which probably was a mixture of all the possible reduction products.

3-Methoxy-4-acetoxypropiophenonylpyridinium Bromide.—From 1 g. of the requisite ketone and 1 ml. of anhydrous pyridine in 20 ml. of dry benzene was obtained according to the usual procedure 0.7 g. (54%) of product which after crystallization from absolute alcohol melted at 209–210°.

Anal. Calcd. for $C_{17}H_{18}BrNO_4$: Br, 21.0. Found: Br, 20.8.

3-Methoxy-4-acetoxypropiophenonylpiperidinium Bromide.—This product resulted when a solution of 3 g. of the appropriate ketone, 5 ml. of dry piperidine, and 30 ml. of anhydrous benzene was refluxed for fifteen minutes. The precipitate (3 g., 80%) on crystallization from absolute alcohol melted at 239–240°.

Anal. Calcd. for $C_{17}H_{23}BrNO_4$: Br, 20.7. Found: Br, 20.3.

β-(3-Methoxy-4-acetoxyphenyl)-β-hydroxyisopropylpyridinium Bromide (IV).—The reduction of 1.2 g. of 3-methoxy-4-acetoxypropiophenonylpyridinium bromide in 9 ml. of water was accomplished in the presence of 100 mg. of platinum oxide similarly to the reductions previously described. After 1 mole of hydrogen had been absorbed, the catalyst and solvent were removed to obtain a solid material which on crystallization from absolute ethanol yielded 0.6 g. of material melting at 223–224°. From the mother liquor was obtained by addition of ether another crop of crystals which indicated no depression on mixed melting point with a sample of the material first obtained. A total yield of 0.9 g. (75%) of purified material resulted. On evaporation of the mother liquor an uncrystallizable oil resulted. With the starting material and with 3-methoxy-4-acetoxypropiophenonylpiperidinium bromide a strong depression of melting point was noted.

In another experiment the reduction was attempted at ordinary pressures. After four hours, only starting material was recovered.

Anal. Calcd. for $C_{17}H_{20}BrNO_4$: Br, 20.9. Found: Br, 20.4.

β-(3-Methoxy-4-acetoxyphenyl)-β-acetoxyisopropylpyridinium Bromide.—A vigorous evolution of hydrogen bromide ensued when a solution of 100 mg. of β-(3-methoxy-4-acetoxyphenyl-β-hydroxyisopropylpyridinium bromide in 8 ml. of glacial acetic acid was refluxed with 1 ml. of acetyl bromide for one hour. The light yellow oil which resulted on vacuum removal of the solvent crystallized on trituration with ether. The product (0.11 g.,

(19) L. F. Fieser and E. B. Hershberg, THIS JOURNAL, **58**, 2314 (1936).

94%) after crystallization from absolute ethanol melted at 206°.

Anal. Calcd. for $C_{19}H_{22}BrNO_5$: Br, 18.8. Found: Br, 18.1.

4-(α-Hydroxy-β-bromopropyl)-guaiacol Benzoate.[8]—The preferential hydrolysis of the α-bromine atom of 4-(α,β-dibromopropyl)-guaiacol benzoate was accomplished by refluxing for eighteen hours a solution of 5 g. of the dibromide in 30 ml. of 95% ethanol, 30 ml. of acetone, and 30 ml. of water with 5 g. of calcium carbonate. The filtrate on vacuum concentration yielded an oil whose ether solution was washed well with water, treated with Norit and dried over sodium sulfate. Evaporation of the ether yielded a light yellow, sweet-smelling oil (3.5 g., 83%) which resisted all attempts to induce crystallization, and which could not be distilled at 10^{-5} mm. It analyzed fairly well for the bromohydrin.

Anal. Calcd. for $C_{17}H_{17}BrO_4$: Br, 21.9. Found: Br, 23.2.

An ether solution of this material was allowed to react with pyridine over a period of two months at room temperature. There resulted only a small amount of impure solid which was not further investigated.

Summary

1. A series of four pyridinium analogs of the pressor amines which contain the guaiacol nucleus have been prepared.

2. Conditions have been found which make possible the catalytic reduction of pyridinium ketones to pyridinium alcohols.

3. Conditions have been discovered which render feasible the direct α-haloacylation of guaiacol in the presence of aluminum chloride without demethylation.

EVANSTON, ILLINOIS RECEIVED FEBRUARY 18, 1946

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Ketene Acetals. XVI. Phenylketene Diethyl- and Dimethylacetals from the Pyrolysis of the Corresponding Orthoesters

BY S. M. MCELVAIN AND CALVIN L. STEVENS[1]

Orthoesters containing certain negative substituents on the α-carbon readily pyrolyze with the loss of alcohol to the corresponding ketene acetals. The first report of such behavior was the isolation of carbethoxyketene diethylacetal in an attempt to prepare an orthoester from the iminoester hydrochloride derived from ethyl cyanoacetate.[2] Later, Staudinger and Rathsam[3] reported a similar pyrolysis of ethyl orthophenylacetate to the corresponding ketene acetal during distillation. These authors also noted that considerable amounts of ethyl phenylacetate were formed simultaneously with the ketene acetal in this pyrolysis; they stated that no diethyl ether could be detected among the pyrolysis products indicating that the normal ester did not result from the simple loss of the ether from the orthoester. Staudinger and Rathsam also reported that phenylketene diethylacetal, when heated in a bomb at 260–270°, developed pressure (presumed to be ethylene) and was converted mainly into ethyl phenylacetate; a small amount of a solid, m.p. 136–137°, which was not identified, also was obtained.

More recently Sah, Ma and Kao[4] reported a series of esters of orthophenylacetic acid, prepared by the alcoholysis of the hydrochlorides of methyl and ethyl phenyliminoacetates, but they made no mention of any facile pyrolysis of these orthoesters even when distilled at atmospheric pressure. In fact, these authors report analyses (C and H) that indicate pure orthoesters.

As phenylketene acetals were needed for other work in this Laboratory, a study of their preparation was undertaken and the present paper is a report of some of the unexpected results that were obtained, particularly in connection with the preparation of phenylketene dimethylacetal.

In general the results obtained from the pyrolysis of ethyl orthophenylacetate paralleled those of Staudinger and Rathsam.[3] This orthoester was very difficult to obtain pure and it was only possible to do so by a rapid distillation at low pressure (0.1 mm., b.p. 88–91°). When the orthoester, as obtained from the alcoholysis of the iminoester hydrochloride, was slowly distilled as in a fractional distillation, approximately 70% of the theoretical quantity of alcohol collected in the cold trap and the distillate could be separated into ethyl phenylacetate (20%) and phenylketene diethylacetal (70%), b.p. 86–88° (0.2 mm.). The residue remaining from this distillation was composed of a dimer[5] and a small amount of a white crystalline solid, m.p. 140–141°, which was identified as *meso*-diethyl α,α′-diphenylsuccinate and which undoubtedly corresponds to the material, m.p. 136–137°, isolated by Staudinger and Rathsam.[3] The formation of this compound during the pyrolysis is discussed later in connection with the pyrolysis of methyl orthophenylacetate.

Ethyl phenylacetate is formed by the loss of ethylene (identified as ethylene bromide) during the pyrolysis of the orthoester. Whether it is formed directly from the orthoester or from the

(1) Wisconsin Alumni Research Foundation Research Assistant, 1944–.

(2) (a) Reitter and Weindel, *Ber.*, **40**, 3359 (1907); (b) *cf.* also Glickman and Cope, THIS JOURNAL, **67**, 1017 (1945).

(3) Staudinger and Rathsam, *Helv. Chim. Acta*, **5**, 645 (1922).

(4) Sah, Ma and Kao, *J. Chem. Soc.*, 305 (1931).

(5) This dimer could not be converted by hydrolysis into α,γ-diphenylacetoacetic ester as the dimer of ketene diethylacetal was converted to acetoacetic ester (Johnson, Barnes and McElvain, THIS JOURNAL, **62**, 964 (1940)). Instead, it invariably yielded phenylacetic acid.