TABLE I

Compound[a]	Over-all yield, %	M. p., °C.[b]	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-S-5,6-Dimethylpyrazine	80	261.5–262	$C_{12}H_{14}O_2N_4S$	51.76	5.07	20.16	51.62	4.95	20.31
2-N⁴-Acetyl-S-5,6-dimethylpyrazine		233 –234	$C_{14}H_{16}O_3N_4S + {}^1/_2H_2O$	51.03	5.20	17.02	51.26	4.97	17.38
2-S-5,6-Diphenylpyrazine[c]	41	115	$C_{22}H_{18}O_2N_4S + H_2O$	62.83	4.79	13.33	62.94	5.01	13.50
2-N⁴-Acetyl-S-5,6-diphenylpyrazine		194.5–195	$C_{24}H_{20}O_3N_4S$	64.83	4.54	12.61	64.90	4.22	12.56
2-S-6-Methylpyrazine	68	258 –259	$C_{11}H_{12}O_2N_4S$	49.96	4.58	21.21	50.16	4.74	21.36
2-N⁴-Acetyl-S-6-methylpyrazine[d]		239 –239.5	$C_{13}H_{14}O_3N_4S + {}^1/_2H_2O$	49.49	4.79	17.77	49.56	4.75	17.85
2-S-5-Methylpyrazine	70	237.5–238.5	$C_{11}H_{12}O_2N_4S$	49.96	4.58	21.21	50.20	4.57	21.11
2-N⁴-Acetyl-S-5-methylpyrazine[d]		240 –241	$C_{13}H_{14}O_3N_4S$	50.94	4.61	18.30	51.16	4.97	18.60
2-S-5- or 6-phenylpyrazine	80	270 –271	$C_{16}H_{14}O_2N_4S$	58.88	4.32	17.17	58.82	4.73	17.16
2-N⁴-Acetyl-S-5- or 6-phenylpyrazine		237 –240	$C_{18}H_{16}O_3N_4S$	58.68	4.38		57.95	4.66	

[a] S = sulfanilamido. [b] All m. p. corrected. [c] This sulfa drug dissolves in ether, alcohols, benzene and chloroform. [d] Mixed m. p. between 2-N⁴-acetyl-S-6-methylpyrazine and 2-N⁴-acetyl-S-5-methylpyrazine, 210°.

The mixture was held at 40–50° for two hours and allowed to stand overnight at room temperature. The greater part of the pyridine was distilled off *in vacuo*, and the residue was diluted with 100 cc. of water. The crystalline product was filtered off, washed with water and dried; yield 4.22 g., 81.1%.

Four grams of the crude acetyl compound was hydrolyzed by boiling with a mixture of 30 cc. of alcohol and 15 cc. of concentrated hydrochloric acid under reflux for one hour. The mixture was diluted with 100 cc. of water and 50 cc. of concentrated ammonia water was added in order to effect solution. After decolorizing with a suitable charcoal, the solution was acidified with acetic acid, the crystals were collected, washed thoroughly and dried; yield 3.00 g. of 2-sulfanilamido-5,6-dimethylpyrazine, 86.4%.

The other compounds were obtained in a similar manner. In some cases it was necessary to crystallize the compounds from solvents.

Acknowledgment.—We are indebted to Drs. R. T. Major and J. R. Stevens for their interest and valuable suggestions, and to Mr. J. P. Messerly for technical assistance on some of the experiments. The aid of Messrs. D. F. Hayman, H. Clark, R. N. Boos and Mrs. E. H. Meiss in providing microanalyses is gratefully acknowledged.

Summary

Improved methods for preparing lumazine and derivatives substituted in the 6,7-positions have been described. A degradation reaction for converting lumazine and substituted lumazines to aminopyrazines is recorded which has been utilized for the rapid and convenient preparation of 2-aminopyrazine and 2-aminopyrazines substituted in 5 and 6 positions. On alkaline hydrolysis the lumazines are converted to the corresponding 2-aminopyrazine-3-carboxylic acids which can be decarboxylated to the 2-aminopyrazines. More vigorous alkaline hydrolysis of lumazine and of 2-aminopyrazine-3-carboxylic acid yields 2-hydroxypyrazine-3-carboxylic acid.

From the new aminopyrazines, the corresponding new sulfanilamide compounds and their acetyl derivatives have been prepared.

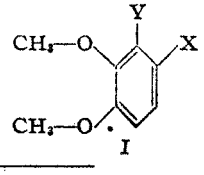
RAHWAY, N. J. RECEIVED FEBRUARY 13, 1945

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Studies in the Veratrole Series

BY RICHARD T. ARNOLD AND NEWMAN BORTNICK[1,2]

Disubstituted veratrole derivatives of type I are not readily available, and in the past these have been obtained by the degradation of certain alkaloids[3] or by tedious indirect synthetic methods. Direct nuclear substitution usually gives rise to the exclusive formation of compounds related to II.[4]



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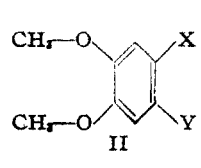


II

Carboxyl groups often undergo replacement during aromatic substitution reactions when they occupy a position ortho or para to an alkoxyl group. On the contrary, ester groups are not eliminated unless they are converted to carboxyl during the course of the reaction. By applica-

(1) Abstracted from the Ph.D. thesis of Newman M. Bortnick which was accepted by the Graduate Faculty in February, 1944.

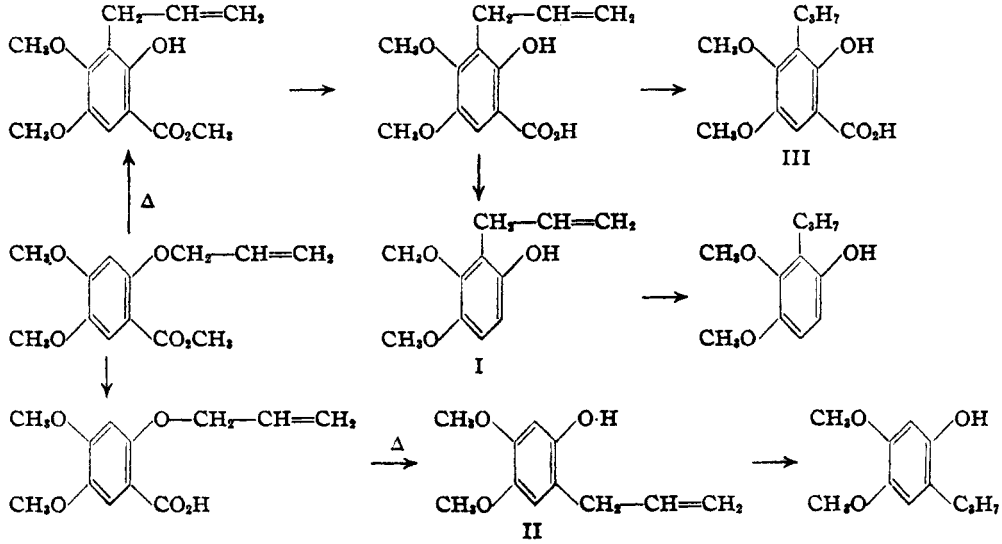
(2) Sharp and Dohme Fellow, 1942–1944.

(3) Haworth, Perkin and Stevens, *J. Chem. Soc.*, 1764 (1926).

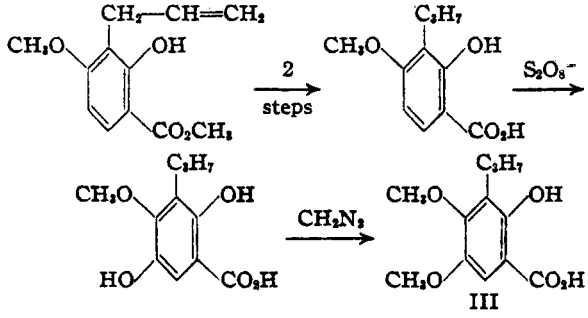
(4) Arnold and Bordwell, THIS JOURNAL, **64**, 2983 (1942).

tion of these facts, we have devised a synthesis of veratrole derivatives of types I and II (Y = allyl, and X = hydroxyl) from a common intermediate. These materials are valuable intermediates in the synthesis of *o*-cyanophenols to be used in future experiments in this Laboratory.

A summary of the reactions employed is:



Confirmation of the formula assigned to III was obtained by an independent synthesis from well known starting materials[5] by taking advantage of the direct introduction of phenolic hydroxyl groups by means of persulfate oxidation.[6]



Acknowledgment.—The authors wish to express their appreciation to Sharp and Dohme, Incorporated, for generous financial support and to Drs. James Sprague and Maurice L. Moore for their sincere interest.

Experimental

Methyl 6-Allyloxyveratrate.—Methyl 6-hydroxyveratrate (93.5 g.), allyl bromide (66 g.), anhydrous potassium carbonate (125 g.) and dry acetone (250 cc.) were refluxed and stirred for forty-five hours. After the first twenty-four hours, 6.0 g. of allyl bromide and 10 cc. of acetone were added. The mixture was cooled, filtered, and warmed to remove the excess solvent. Crystallization of the residue from a mixture of petroleum ether (b. p. 28–38°) and ether gave 107 g. of product; m. p. 54–55°

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.88; H, 6.39. Found: C, 62.08; H, 6.65.

5-Allyl-6-hydroxyveratric Acid.—The above allyloxy ester (10 g.) was heated at 200–220° in a nitrogen atmosphere for three hours. Distillation in a sausage flask gave 8.8 g. of product; b. p. 147–154° (5 mm.). Saponification of this crude ester with sodium hydroxide (10%) followed by acidification gave the acid; m. p. 116.5–117.5° after crystallization from dilute acetic acid.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.48; H, 5.92. Found: C, 60.62; H, 6.18.

The methyl ester which was not readily obtained pure by recrystallization of the rearrangement product formed readily when the hydroxy acid was treated with one equivalent of diazomethane; m. p. 37.5–38°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.88; H, 6.39. Found: C, 62.19; H, 6.51.

5-Propenyl-6-hydroxyveratric Acid.—Five grams of 5-allyl-6-hydroxyveratric acid was admixed with powdered potassium hydroxide (40 g.) and heated in a nickel crucible at 210–20° for twenty-five minutes. The product was dissolved in water, acidified and extracted with ether. Evaporation gave only a black viscous oil. When the crude acid was converted to its methyl ester and distilled in a sausage flask at low pressure, a light yellow oil was obtained. This on saponification gave crude 5-propenyl-6-hydroxyveratric acid, m. p. 108–112°. Recrystallization from dilute acetic acid gave 1.5 g. of pure acid; m. p. 113–113.5°.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.52; H, 5.92. Found: C, 60.62; H, 6.15.

5-Propyl-6-hydroxyveratric Acid.—Hydrogenation of 5-allyl-6-hydroxyveratric acid (1.0 g.) in ethanol (95%) with platinum oxide (10 mg.) was rapid and the theoretical quantity of hydrogen was absorbed. After removing the catalyst by filtration and evaporating the solvent, a residue formed which was readily crystallized from dilute acetic acid; m. p. 116.5–117.5°. This acid markedly depressed the melting point of the corresponding allyl derivative.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 60.00; H, 6.71. Found: C, 59.95; H, 6.40.

3-Allyl-4-hydroxyveratrole.—When 5-allyl-6-hydroxyveratric acid was treated with an equal quantity of dimethylaniline and heated at reflux temperature for twenty minutes the evolution of carbon dioxide was completed Removal of the dimethylaniline in the usual way gave a residue which distilled at 168–175° (24 mm.); yield 84.5%.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26 Found: C, 68.01; H, 7.54.

(5) Arnold and Moran, THIS JOURNAL, **64**, 2986 (1942).

(6) Baker and Savage, *J. Chem. Soc.*, 1602 (1938).

Hydrogenation of this product in methanol in the presence of Adams catalyst was complete in ten minutes. The 3-propyl-4-hydroxyveratrole so obtained melted at 92–93° after recrystallization from dilute methanol.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.33; H, 8.21. Found: C, 67.30; H, 8.42.

6-Allyloxyveratric Acid.—This acid was obtained from the methyl ester (12.6 g.) by refluxing for one and one-half hours with 500 cc. of potassium hydroxide (5%); wt. 10.2 g.; m. p. 123.5–124° after recrystallization from dilute acetic acid.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.48; H, 5.92. Found: C, 60.76; H, 6.03.

4-Hydroxy-5-allylveratrole.—Nine grams of 6-allyloxyveratric acid was refluxed for one hour with dimethylaniline (9.0 g.). A quantitative amount of carbon dioxide was liberated. The reaction mixture was taken up in benzene and the dimethylaniline removed by extraction with hydrochloric acid. Removal of the benzene afforded a residue which distilled at 143–145° (2 mm.); wt. 6.7 g. This product solidified in the receiver; m. p. 38–41°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.60; H, 7.51.

4-Hydroxy-5-propylveratrole.—This product was obtained by catalytic reduction of 4-hydroxy-5-allylveratrole (1.5 g.) in methanol (10 cc.) by the use of Adams catalyst (10 mg.), m. p. 70.5–72°.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.35; H, 8.21. Found: C, 67.87; H, 8.01.

Methyl 3-Propyl-4-methoxysalicylate.—Catalytic hydrogenation of methyl 3-allyl-4-methoxysalicylate[5] (106 g.) dissolved in warm methanol (150 cc.) was brought about quantitatively in twenty-five minutes in the presence of Adams catalyst (300 mg.); m. p. 58–59° after crystallization from dilute methanol.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.33; H, 7.19. Found: C, 64.33; H, 7.45.

Saponification of the ester (45 g.) with potassium hydroxide (400 cc., 10%) and ethanol (50 cc.) gave 3-propyl-4-methoxysalicylic acid (33.3 g.); m. p. 168–170° (dec.).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.90; H, 6.71. Found: C, 62.68; H, 6.85.

2,5-Dihydroxy-3-propyl-4-methoxybenzoic Acid.—Twenty-one grams of 3-propyl-4-methoxysalicylic acid was dissolved in aqueous sodium hydroxide (10 g. in 80 cc.). To this was added simultaneously (a), a solution of sodium hydroxide (20 g. in 60 cc.), and (b), a warm aqueous solution of potassium persulfate (34 g. in 400 cc.) over a period of forty minutes. The color of the solution changed from light amber to permanganate purple. After forty-two hours the solution was acidified to congo red and extracted three times with ether to remove unchanged starting material. The aqueous solution was treated with concentrated hydrochloric acid (30 cc.) and heated to boiling. The product precipitated on cooling and was recrystallized from benzene; wt. 6.0 g. (56% based on starting material used); m. p. 164.5–165.5°.

Anal. Calcd. for $C_{11}H_{14}O_5$: C, 58.45; H, 6.24. Found: C, 58.31; H, 6.34.

When this acid was treated with diazomethane in ether there was obtained a crude ester which on saponification gave 5-propyl-6-hydroxyveratric acid; m. p. 114.5–116.5°. This sample was identical with that obtained by an independent route as described above.

Summary

It has been shown that isomeric pairs of 3,4- and 4,5-disubstituted veratroles can be readily prepared from a common intermediate by means of the Claisen rearrangement of phenyl allyl ethers.

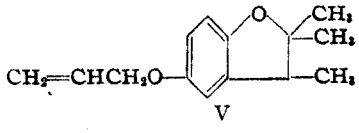
MINNEAPOLIS, MINNESOTA RECEIVED FEBRUARY 14, 1945

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

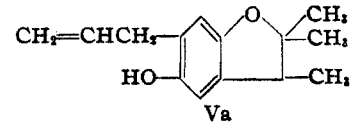
The Rearrangement of Phenyl Allyl Ethers. IX. 2,2,3-Trimethyl-5-allyloxycoumaran[1]

BY WALTER M. LAUER AND EDGAR E. RENFREW[2]

The thermal rearrangement of 2,2,3-trimethyl-5-allyloxycoumaran, V, yields 2,2,3-trimethyl-5-hydroxy-6-allylcoumaran, Va. This finding is in accord with predictions based on the Mills–Nixon effect. Evidence for the structures assigned to the allyl ether, V, and to its rearrangement product, Va, follows.

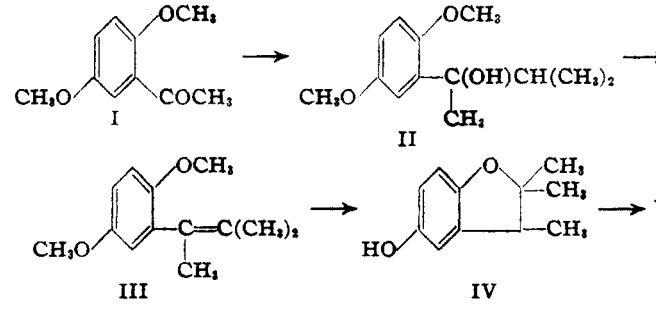


V



Va

The synthesis of 2,2,3-trimethyl-5-allyloxycoumaran was accomplished in a manner similar to that described[3] for the preparation of 2,2,3-trimethylcoumaran. The starting point for the present synthesis was 2,5-dimethoxyacetophenone, I, and the following outline shows the transformations which were involved in the synthesis of the allyl ether, V.



I II III IV V

The rearrangement of V was carried out in an atmosphere of nitrogen at a temperature of 215–

(1) Paper VIII, THIS JOURNAL, **65**, 289 (1943).

(2) Abstract of Ph.D. Thesis submitted in February, 1944.

(3) Lauer and Moe, THIS JOURNAL, **65**, 291 (1943).