TABLE I

ESTERS OF β-METHOXY-β-PHENYLPROPIONIC ACID

Ester	Yield, %	B. p., °C.	$n^{20}D$	d^{20}_4	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Ethyl[a]	75	100–106 (1.5)	1.4975	1.050	69.21	68.97	7.75	8.05
2-Ethylhexyl	65	156–159 (2.5)	1.4868	0.981	73.93	73.73	9.65	9.99
n-Tetradecyl	52	185–190 (2.5)	1.4780	.939	76.55	76.64	10.71	10.30
n-Heptadecyl	60	200–212 (2.0)	1.4818	.941	77.46	77.79	11.08	11.36

[a] Saponification of the ethyl ester in diethylene glycol[16] gave ethanol and cinnamic acid. Apparently methanol is eliminated during the strenuous hydrolysis.

β,β,β-Triphenylpropionic Acid.—The crude acid chloride was hydrolyzed with 10% sodium hydroxide solution. The aqueous solution was washed with ether and acidified. The over-all yield, from triphenylchloromethane, of crude, yellow β,β,β-triphenylpropionic acid was 55%. For analysis, the crude acid was dissolved in hot absolute ethanol, treated with Darco, and then recrystallized twice from absolute ethanol. The recovery was 43%. This material had a capillary melting point of 177–178° with preliminary "sintering." On a microscope hot stage the acid began subliming slightly to a melt at 165° and was subliming rapidly at 179.5°. It melted at 180–181.5° (cor.).[18]

Anal. Calcd. for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00; neut. equiv., 302. Found: C, 83.55; H, 6.41; neut. equiv., 299.

Ethyl β,β,β-Triphenylpropionate.—Crude β,β,β-triphenylpropionyl chloride was dissolved in twice its weight of absolute ethanol and the solution was refluxed for twenty hours. Water was added and the ester was extracted into ether. Distillation of the residue from the ether, at 203–208° at 3 mm., gave a 67% yield of the ethyl ester. The product soon crystallized in the receiver; m. p. 65–77°. Recrystallized once from 95% ethanol, it had a capillary melting point of 79–80°. For analysis, a sample was recrystallized again from 95% ethanol. The recovery from the two recrystallizations was 72%. The analytical sample melted on a microscope hot stage at 81–82°[19] (cor.). The crystals of ethyl β,β,β-triphenylpropionate were optically anisotropic and showed parallel extinction in all views observed.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71. Found: C, 83.86; H, 6.85.

Butyl β,β,β-Triphenylpropionate.—β,β,β-Triphenylpropionyl chloride was dissolved in an equal weight of *n*-butanol and the solution was refluxed two hours. The product was distilled: b. p. 160–165° at 0.15 mm. A sample was redistilled for analysis: $n^{20}D$ 1.5875; d^{20}_4 1.097.

Anal. Calcd. for $C_{25}H_{26}O_2$: C, 83.76; H, 7.31. Found: C, 84.31; H, 7.48.

(18) Henderson, ref. 8, and Fosse, ref. 9, reported the m. p. as 177° and 178–179°, respectively.

(19) Henderson, ref. 8, reported the m. p. as 81°.

Summary

1. α,β-Dichloroethyl ethyl ether, α-chlorobenzyl methyl ether, and triphenylchloromethane react with ketene to give the corresponding substituted acetyl chlorides. No catalyst is required to effect the reaction with α-chlorobenzyl methyl ether or with triphenylchloromethane in nitrobenzene. The reaction with α,β-dichloroethyl ethyl ether and with triphenylchloromethane in benzene takes place only in the presence of a catalyst such as aluminum chloride.

2. Benzyl chloride, benzyl bromide, benzotrichloride, benzoyl chloride, chloroacetone, and 2-chloro-2-nitropropane failed to react with ketene under the conditions used.

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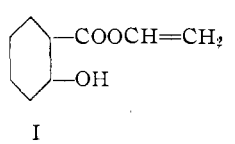
[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT OF THE MONSANTO CHEMICAL COMPANY]

2-Methyl-4-keto-1,3-benzodioxanes from Salicylic Acids and Vinyl Acetate

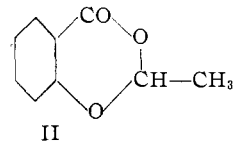
BY DAVID T. MOWRY, WILLIAM H. YANKO AND EUGENE L. RINGWALD

The preparation of vinyl salicylate (I) was attempted by the mercuric acetate catalyzed ester-interchange method of Hermann and Haehnel[1] using salicylic acid and vinyl acetate as the reagents. The product, obtained in 53% yield, boiled in the expected range, but solidified after long standing and melted at 33° after recrystallization from alcohol. This behavior seemed anomalous since vinyl esters ordinarily melt lower than the corresponding methyl esters and methyl salicylate is reported to melt at −8°.

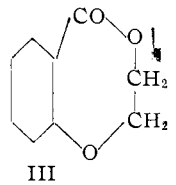
Further investigation showed that the compound did not rapidly decolorize bromine water, give a color with ferric chloride solution, or generate methane when dropped into an ether solution of methylmagnesium iodide. An examination of the infrared spectrum revealed the absence of the



I



II



III

(1) Hermann and Haehnel, U. S. Patent, 2,245,131 (1941), *C. A.*, **35**, 5908 (1941).

characteristic hydroxyl band at 3.1 μ which has shown to be present in anhydrous methyl salicylate and *o*-cresol control samples (see Fig. 1[2]).

These results suggested that a cyclization had taken place in which both the vinyl and phenolic hydroxyl functions had been eliminated. The formation of a seven-membered ring structure (III) instead of the expected 2-methyl-4-keto-1,3-benzodioxane (II) was eliminated as a possibility when it was found that acetaldehyde and salicylic acid were regenerated when the compound was saponified with sodium hydroxide.

It was assumed that this reaction proceeded in two stages, the first being the formation of α-acetoxyethyl salicylate, and the second being a cyclization of the intermediate with the elimination of acetic acid. This route has been demonstrated by an alternate synthesis in which the intermediate was isolated. When a suspension of sodium salicylate in methyl ethyl ketone was refluxed with α-chloroethyl acetate in the presence of a little potassium iodide, α-acetoxyethyl salicylate was obtained in fair yield. The success of this reaction is of interest in view of the report of French and Adams[3] that definite products could not be isolated from the reaction of alkali metal salts of organic acids with compounds such as phenylchloromethyl benzoate. The α-acetoxyethyl salicylate was cyclized in good yield to give 2-methyl-4-keto-1,3-benzodioxane which was identical with that obtained from the first reaction.

Since the parent compound in this series, 4-keto-1,3-benzodioxane, m.p. 53–54°, had been prepared by Calvet and Carnero[4] by the permanganate oxidation of 1,3-benzodioxane, the above series of reactions was repeated using chloromethyl acetate and sodium salicylate. The intermediate acetoxymethyl salicylate was then cyclized as before to give a sample of 4-keto-1,3-benzodioxane which had the same melting point as that previously recorded. This verified by analogy the structure assigned to the salicylic acid–vinyl acetate reaction product, and incidentally afforded an improved synthesis of the parent compound.

The reaction with vinyl acetate has been extended to a number of nuclearly substituted salicylic acids including 5-nitro-, 5-chloro-, 5-bromo-, 3-methyl-, 3-methoxy-, 3-methyl-5-chlorosalicylic acids as well as to 2-hydroxy-3-naphthoic acid with the formation of the corresponding 2-methyl-4-keto-1,3-benzodioxanes. At least 100% excess of vinyl acetate is desirable since the acetic acid liberated in the ring closure is taken up by the excess vinyl acetate with the formation of ethylidene diacetate.

(2) See Buswell, Dietz and Rodebush, *J. Chem. Phys.*, **5**, 50 (1937). The authors are indebted to Dr. Dexter H. Reynolds and his collaborators, Mr. J. A. Rich, Mr. D. R. Baesecker and Miss Rosella Ulm, of these Laboratories, for conducting the infrared investigation.

(3) French and Adams, THIS JOURNAL, **43**, 651 (1921).

(4) Calvet and Carnero, *Anales soc. espan. fis. quim.*, **30**, 445 (1932).

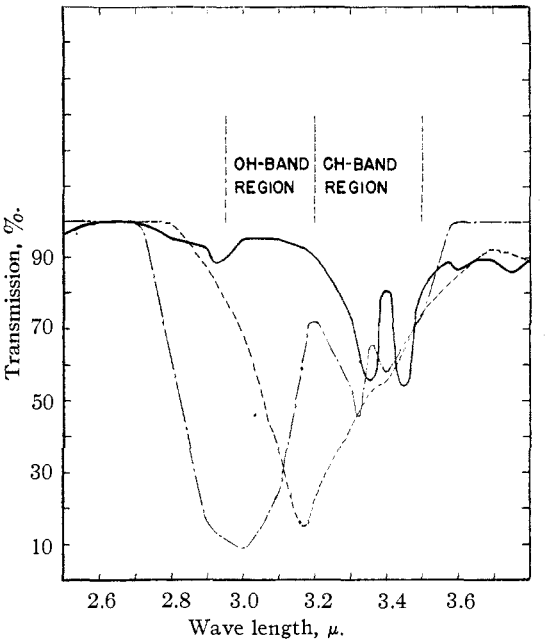


Fig. 1.—Infrared absorption spectra in carbon tetrachloride solution of: —, 2-methyl 4-keto-1,3-benzodioxane (50%); —·—, ortho cresol (50%); ------, methyl salicylate (50%).

The reaction has also been found to proceed with thiosalicylic acid to give good yields of 2-methyl-4-keto-1,3-benzothioxane. Furthermore a vigorous reaction has been observed between salicylamide and vinyl acetate which results in the formation of 2-methyl-4-keto-1,3-benzoxazine, although this compound is more advantageously prepared by the method of Hicks[5] who treated salicylamide with paraldehyde in the presence of hydrochloric acid as a catalyst.

A similar reaction between anthranilic acid and vinyl acetate failed. In this connection, it was observed that, while aldehydes are known to give Schiff bases with anthranilic acid, benzaldehyde reacted smoothly with N-methyl-anthranilic acid in refluxing benzene solution in the presence of a trace of hydrochloric acid to give 1-methyl-2-phenyl-4-keto-3,1-benzoxazine.

That the reaction proceeds as well for α-hydroxy aliphatic acids as it does with *o*-hydroxybenzoic acids was shown by the formation of 2-methyl-4-keto-5-phenyl-1,3-dioxolane from mandelic acid and vinyl acetate. This was analogous to the known reaction of glycolic acid[6] with acetylene in the vinylation reaction to give 2-methyl-4-keto-1,3-dioxolane instead of vinyl glycolate.

The reaction has been further extended by the substitution of isopropenyl acetate for vinyl acetate with the subsequent formation of 2,2-dimethyl-4-keto-1,3-benzodioxane. In this case the yield was poor and the excess isopropenyl acetate was simultaneously converted to acetone and

(5) Hicks, *J. Chem. Soc.*, **97**, 1032 (1910).

(6) Conway, U. S. Patent 2,370,779 (1945).

TABLE I

4-Keto-1,3-benzodioxanes	Formula	Yield,[b] %	M. p., °C.	B. p., °C.	Mm.	Analyses,[a] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
2-Methyl-	$C_9H_8O_3$	60	33	97–98	1	65.8	65.8	4.91	5.01
2,2-Dimethyl-	$C_{10}H_{10}O_3$	20	58–59	112–114	4	67.4	67.7	5.63	5.87
2,8-Dimethyl-	$C_{10}H_{10}O_3$	25	86–87	164–166	25	67.4	67.4	5.63	5.64
2-Methyl-6-chloro-	$C_9H_7ClO_3$	45	95–96	160	7	54.8	54.7	3.98	3.53[c]
2-Methyl-6-bromo-	$C_9H_7BrO_3$	14	84–85	148–150	5	44.5	44.6	2.88	3.10
2,8-Dimethyl-6-chloro-	$C_{10}H_9ClO_3$	15	130	.....	..	56.5	56.6	4.23	4.43
2-Methyl-6-nitro-	$C_9H_7NO_5$	17[d]	111–112	182	4	51.7	51.7	3.35	3.42
2-Methyl-8-methoxy-	$C_{10}H_{10}O_4$	49	81	152–154	2	61.9	62.1	5.19	5.28
2-Methyl-4-keto-naphtho-[*b*]-1,3-dioxane	$C_{13}H_{10}O_3$	41	91–92	185	2	72.9	73.2	4.67	5.09
Other compounds									
2-Methyl-4-keto-1,3-benzothioxane	$C_9H_8SO_2$	69	57	147	5	60.0	60.1	4.45	4.76[e]
2-Methyl-4-keto-5-phenyl-1,3-dioxolane	$C_9H_{10}O_3$	77	.....	154	21[f]	67.8	67.5	5.08	5.27
1-Methyl-2-phenyl-4-keto-3,1-benzoxazine	$C_{15}H_{13}NO_2$	80	105	.....	..	75.6	75.3	5.48	5.61[g]

[a] Microanalyses by the Arlington Laboratories, Fairfax, Va. [b] Yield of pure product. Crude yields were often much higher. [c] Calcd. for Cl: 17.87. Found: 17.62. [d] Yield low because of explosion during distillation. [e] Calcd. for S: 17.75. Found: S, 17.90. [f] $n^{25}D$ 1.5112. [g] Calcd.: N, 5.86. Found: N, 6.05.

acetic anhydride, because of the inherent instability of the intermediate ketone diacetate.

The properties of the various unreported heterocyclic compounds prepared are listed in Table I.

A search of the literature for other compounds of this type revealed that Wallach[7] and Böeseken[8] had reported that the chloralide of salicylic acid, 2-trichloromethyl-4-keto-1,3-benzodioxane, had been obtained "in poor yield" by refluxing salicylic acid for five hours with excess chloral, although Shah and Alimchandi[9] had been unable to isolate any product by this method. The latter investigators found that the introduction of hydrogen chloride or acetic acid into the system had no beneficial effect, while sulfuric acid caused the reaction to take an entirely different course, namely, alkylation of the ring in a position para to the hydroxyl group.

In the present work, also, the earlier results of Böeseken could not be duplicated, but it was found that the introduction of an excess of thionyl chloride into the above system gave a vigorous evolution of sulfur dioxide and hydrogen chloride and that a moderate yield of the desired chloralide was easily obtained. An attempt to prepare the trichloromethyl compound by reaction of chloral diacetate with salicylic acid was unsuccessful.[10]

Experimental

Intermediate Acids.—The following procedure was employed for the preparation of 2-methyl-5-chlorosalicylic acid: Into a solution of 455 g. (3.0 moles) of *o*-cresotinic acid in 3 liters of glacial acetic acid was passed a vigorous stream of chlorine until 238 g. (10% excess) had been absorbed. The temperature was diluted with an equal volume of water, cooled to 0° and filtered. Recrystallization of the product from dilute ethanol gave 434 g. (78% yield) of 2-methyl-5-chlorosalicylic acid, m. p. 225°.

Anal. Calcd. for $C_8H_7O_3Cl$: C, 51.50; H, 3.75; Cl; 19.02; neut. equiv., 186.6. Found: C, 51.61; H, 3.88, Cl, 18.73; neut. equiv., 186.3.

In a similar fashion were prepared 5-chlorosalicylic acid,[11] m. p. 171°, in 75% yield and 5-bromosalicylic acid,[12] m. p. 166°, in 50% yield by halogenation of salicylic acid.

3-Methoxysalicylic acid, m. p. 147°, was prepared by the alkali fusion[13] of *o*-vanillin.

5-Nitrosalicylic acid, *o*-cresotinic acid, 2-hydroxy-3-naphthoic acid, mandelic acid and thiosalicylic acid were obtained from Eastman Kodak Co.

2-Methyl-4-keto-1,3-benzodioxanes from Vinyl Acetate.—Salicylic acid (138 g., 1.0 mole), vinyl acetate (259 g., 3.0 moles), mercuric acetate (4.0 g.), sulfuric acid (0.5 cc.) and hydroquinone (1.0 g.) were refluxed thirty-six hours before distilling the excess vinyl acetate and the acetic acid at 200 mm. pressure. The residue was distilled through a 50-cm. Vigreux column taking the fraction b. p. 153–160° (30 mm.). Two redistillations gave 87 g. (53%) of nearly pure product, b. p. 97–98° (1 mm.), $n^{25}D$ 1.5380, which solidified on long standing at room temperature. On later runs, the material crystallized promptly when seeded. Recrystallization from dilute ethanol gave monoclinic prisms, m. p. 32–33°, $n^{25}D$ 1.5398 (supercooled).

A 5-g. sample was hydrolyzed by refluxing with alcoholic potassium hydroxide. The effluent gas was identified as acetaldehyde by its odor and by the characteristic blue color it formed with piperidine and sodium nitroprusside. Acidification of the residue precipitated salicylic acid, which was identified by a mixed melting point determination with an authentic sample.

The other acids mentioned above were treated in a similar fashion and the results are given in Table I.

2-Methyl-4-keto-1,3-benzodioxane from α-Acetoxyethyl Salicylate.—Chloroethyl acetate, b. p. 112–116°, was prepared by the method of Ulich and Adams[14] in 65% yield. One mole (122.5 g.) of this material was refluxed for fifty hours with 160 g. (1.0 mole) of sodium salicylate and 2 g. of potassium iodide in 400 cc. of methyl ethyl ketone. The product was poured into several volumes of water and extracted with ether. The ether extract was washed with dilute sodium carbonate, water and dilute hydrochloric acid, and distilled rapidly to give 122 g. of crude product, b. p. 120–130° (2–3 mm.). Careful refractionation at high reflux ratio through a 50-cm. Vigreux column gave 74 g., 33%, of purer material, b. p. 106–107° (1.0 mm.), $n^{25}D$ 1.5072, which gave a typical violet color with ferric chloride solution.

(7) Wallach, *Ann.*, **193**, 41 (1878).

(8) Böeseken, *Verslag. Akad. Wetenschappen Amsterdam*, **35**, 1084 (1926).

(9) Shah and Alimchandi, *J. Indian Chem. Soc.*, **13**, 475 (1936).

(10) Mowry, THIS JOURNAL, **69**, 2362 (1947).

(11) Earle and Jackson, *ibid.*, **28**, 109 (1906).

(12) Robertson, *J. Chem. Soc.*, **81**, 1480 (1902).

(13) Rupp and Linck, *Arch. Pharm.*, **253**, 33 (1915).

(14) Ulich and Adams, THIS JOURNAL, **43**, 660 (1921).

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.9; H, 5.39. Found: C, 58.79; H, 5.35.

α-Acetoxyethyl salicylate (52 g., 0.25 mole) and 0.2 cc. of concentrated sulfuric acid were heated in a water-bath held at 80° while acetic acid was removed as formed by distillation at 30 mm. through a Vigreux column. In three hours the material had lost 13.5 g. in weight (theoretical for 0.25 mole acetic acid, 15 g.). Distillation gave 33 g. of 2-methyl-4-keto-1,3-benzodioxane, b. p. 108° (3.0 mm.), which solidified at room temperature when seeded. The melting point, 32.5–33.0°, was not depressed by mixing the product from the first preparation.

4-Keto-1,3-benzodioxane from Acetoxymethyl Salicylate.—Chloromethyl acetate, b. p. 112–114°, was prepared in 62% yield by the method of Ulich and Adams.[14] This was caused to react with sodium salicylate in a manner similar to that described above. A 64% yield of acetoxymethyl salicylate, b. p. 106–107° (1.0 mm.), $n^{25}D$ 1.5212, was obtained. The product gave a strong violet color in ferric chloride solution.

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.2; H, 4.80. Found: C, 56.99; H, 4.82.

Acetoxymethyl salicylate (213 g., 1.03 moles) and 0.4 cc. of sulfuric acid were heated in a bath at 115–120° under a short column at 30 mm. pressure. After three hours the theoretical amount of acetic acid had been distilled out and the product was distilled rapidly at 100–105° at 1.5 mm. Refractionation of the crude material gave 120 g., b. p. 99–103° (1.0 mm.), which was partially solid. Recrystallization from dilute ethanol gave 42 g. (28%) of pure material, m. p. 53°.[15]

2,2-Dimethyl-4-keto-1,3-benzodioxane.—The ketene generator, similar to that described by Hurd,[16] which contained a spiral coil constructed of 15 feet of 20 gage Chromel A wire, was capable of producing about 0.6 mole of ketene per hour. When the exit gases were passed into a well-stirred solution of 2.8 cc. of concentrated sulfuric acid in 435 g. of acetone at 50° for eight hours, there resulted on distillation 225 g. (46%) of isopropenyl acetate,[17] b. p. 96–97°, and 80 g. of residue (33% calculated as diketene).

A mixture of 207 g. (1.5 moles) of salicylic acid, 450 g. of (4.5 moles) isopropenyl acetate, 6 g. of mercuric acetate and 0.7 cc. of sulfuric acid were refluxed for five hours. Distillation gave 165 g. of acetone, b. p. 54–57°, 25 g. of isopropenyl acetate, b. p. 92–96°, 126 g. of acetic anhydride, b. p. 40–45° (20 mm.), 75 g. (31%) of crude 2,2-dimethyl-4-keto-1,3-benzodioxane, b. p. 110–120° (4 mm.) which solidified on standing. Recrystallization from dilute ethanol gave a product, m. p. 58–59°. Of the isopropenyl acetate consumed, 60% was converted to acetone and 50% to acetic anhydride.

2-Methyl-4-keto-1,3-benzoxazine.—Salicylamide (137 g., 1.0 mole) and vinyl acetate (258 g., 3.0 moles), were refluxed gently in the presence of 4 g. of mercuric acetate and 0.5 cc. of concentrated sulfuric acid. A vigorous exothermic reaction ensued in about ten minutes. After it had subsided, the material was refluxed an additional two hours before distillation under reduced pressure. The crude product, b. p. 140–143° (1.5 mm.), melted at 114–115° after recrystallization from ethanol. It was then triturated with cold sodium hydroxide solution. The insoluble material was removed by filtration and recrystallized from ethanol to give 41 g. of 2-methyl-4-keto-1,3-benzoxazine, m. p. 145–146°. This was not depressed when mixed with an authentic sample prepared by the method of Hicks.[5]

Acidification of the sodium hydroxide solution gave a 50% recovery of salicylamide.

1-Methyl-2-phenyl-4-keto-3,1-benzoxazine.—A solution of 60.5 g. (0.4 mole) of N-methylanthranilic acid, 42 g. (0.4 mole) of benzaldehyde and 1 cc. of concentrated hydrochloric acid in 150 cc. of benzene was refluxed for five hours, while 7 cc. of water was removed in a Dean and Stark trap. Addition of hexane to the cooled solution gave an 80% yield (77 g.) of crude product, m. p. 93–95°. After several recrystallizations from benzene–hexane the material melted at 105°. An attempt to crystallize the material from hot dilute ethanol resulted in hydrolysis and regeneration of the starting materials.

2-Trichloromethyl-4-keto-1,3-benzodioxane.—Sixty-nine grams of salicylic acid (0.5 mole) and 110 g. of chloral 43 cc. (0.6 mole) of thionyl chloride was added dropwise and the mixture refluxed overnight, by which time the evolution of sulfur dioxide and hydrogen chloride had abated. The resultant oil was taken up in ether and washed well with water and 10% sodium carbonate. After drying over calcium chloride, the ether solution was evaporated leaving 70 g. of an oil that still smelled strongly of chloral. After two days in a vacuum oven at 60°, the oil was taken up in ether and a crystalline solid was precipitated by the addition of hexane, giving 29 g. (20%) of white crystals, m. p. 118–121°. Recrystallization from dilute ethanol gave a product, m. p. 124° (literature[7,8] value, 124–125°). When the treatment with thionyl chloride was omitted, only a trace of alkali insoluble material was retained in the ether layer.

Summary

2-Methyl-4-keto-1,3-benzodioxane has been prepared by two methods: (a) from salicylic acid and vinyl acetate, and (b) from sodium salicylate and α-chloroethyl acetate followed by ring closure of the intermediate α-acetoxyethyl salicylate.

Acetoxymethyl salicylate has been similarly prepared and converted to 4-keto-1,3-benzodioxane.

A number of salicylic acid derivatives have reacted with vinyl acetate to give the corresponding 2-methyl-4-keto-1,3-benzodioxanes. An analogous reaction was found to take place with salicylamide, mandelic acid and thiosalicylic acid, giving the benzoxazine, phenyl dioxolane and benzothioxane respectively. A similar reaction was found to take place between isopropenyl acetate and salicylic acid.

N-Methylanthranilic acid was condensed with benzaldehyde to give 1-methyl-2-phenyl-4-keto-3,1-benzoxazine.

An improvement in the preparation of 2-trichloromethyl-4-keto-1,3-benzodioxane has been reported.

DAYTON, OHIO RECEIVED JANUARY 31, 1947

(15) Calvet and Carnero, ref. 4, reported m. p. 53–54° for a product obtained from *p*-nitrophenol in about 10% over-all yield through a four-step synthesis.

(16) Hurd, *J. Org. Chem.*, **5**, 122 (1940).

(17) This is the method of Gwynn and Degering, THIS JOURNAL, **64**, 2216 (1942).