

The 6-acetaminoindole was also obtained in good yield by treating an aqueous solution of 6-aminoindole hydrochloride with acetic anhydride and sodium acetate.⁸

Acknowledgment.—The authors wish to express their thanks to the National Cancer Institute of Canada for their continued support.

(8) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y.

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Acylation of Alkyl Aryl Ethers with Iodine as Catalyst

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Acylation with iodine as a catalyst,^{1,2} gives good yields of some alkoxy-substituted aceto-, propio-, isobutyro-, butyro- and caprophenones, although the acetylation of phenyl acetate, guaiacol, guaiacol acetate and bromo- and iodobenzene is unsuccessful. We have confirmed the report that anisole does not react with succinic anhydride in the presence of iodine.³ The preparation of 4-methoxyacetophenone, reported by Chodroff and Klein,³ who used a mole excess of anisole, has been improved.

Our experiments and those of Kaye, *et al.*,⁴ indicate that iodine can be used as a catalyst for the acylation of aromatic ethers by aliphatic or aromatic monocarboxyl chlorides or anhydrides, and that this method is better for the preparation of alkoxy aryl ketones than the conventional Friedel-Crafts procedure. In successful acylations, the violet colored vapor of the refluxing mixture disappeared after 15–30 minutes, but when there was no reaction, the color persisted.

Experimental⁵

General Procedure, 4-Methoxyacetophenone.—A mixture of 21.6 g. (0.2 mole) of anisole, 22.5 g. (0.22 mole) of acetic anhydride and 1.0 g. (0.004 mole) of iodine was refluxed for three hours. The dark brown solution was poured into 100 ml. of water. The mixture was extracted with ether; the ether solution was washed successively with dilute sodium carbonate, sodium bisulfite and water and then dried over sodium sulfate. After removal of the solvent and distillation of the residue under vacuum, 24 g. (80%) of 4-methoxyacetophenone was obtained, b.p. 120–125° (5 mm.). The yield was 50% when acetyl chloride was used. After crystallization from aqueous methanol the compound melted at 37–38° and its semicarbazone at 197–198°; reported m.p. 38°, semicarbazone m.p. 198–198.5°.³

In the presence of 0.8 g. (0.00278 mole), 1.2 g. (0.0047 mole), 1.6 g. (0.0063 mole), 0.2 g. (0.00079 mole) of iodine, a mixture of 0.2 mole of anisole and 0.22 mole of acetic anhydride, gave yields of 68.7, 66, 61.2 and 45%, respectively.

2-Methoxy-1-acetylnaphthalene.—A mixture of 15.8 g. (0.1 mole) of 2-methoxynaphthalene, 11.3 g. (0.11 mole) of acetic anhydride and 0.5 g. (0.00196 mole) of iodine gave after recrystallization from dilute alcohol, 13.2 g. (63%) of 2-methoxy-1-acetylnaphthalene, m.p. 57°; its mixed m.p. with an authentic specimen was 57–58°; reported by Noller and Adams,⁶ 57–58°.

(1) H. D. Hartough and A. I. Kosak, *THIS JOURNAL*, **68**, 2639 (1946).

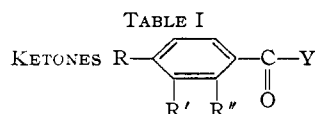
(2) A. I. Kosak and H. D. Hartough, *ibid.*, **69**, 3144 (1947).

(3) S. Chodroff and H. C. Klein, *ibid.*, **70**, 1647 (1948).

(4) I. A. Kaye, H. C. Klein and W. J. Burlant, *ibid.*, **75**, 745 (1953).

(5) The melting points are uncorrected.

(6) C. R. Noller and R. Adams, *THIS JOURNAL*, **46**, 1889 (1924).



R ^a	R'	R''	Y	Yield, %	M.p., °C.	Semi-carbazone m.p., °C.
CH ₃ O	CH ₃ O	H	Methyl	66.5	47–48 ^b	209–211 ^c
CH ₃ O	H	CH ₃ O	Methyl	71	42–43.5 ^d	211–213 ^e
C ₂ H ₅ O	H	H	Methyl	66	36–37.5 ^f	179–180 ^g
CH ₃ O	H	H	Ethyl	50	26–27 ^h	171–172 ⁱ
CH ₃ O	CH ₃ O	H	Ethyl	46.5	56–58 ^j	191 ^k
C ₂ H ₅ O	H	H	Ethyl	57	29–30 ^l	181–183 ^m
CH ₃ O	H	H	Propyl	68	19–21 ⁿ	179–181 ^o
CH ₃ O	CH ₃ O	H	Propyl	74	59–61 ^p	178–180 ^q
CH ₃ O	H	H	<i>i</i> -Propyl	42	^r	202–203 ^s
CH ₃ O	H	H	Pentyl	49.3	38–39 ^t	143 ^u

^a All compounds were recrystallized from aqueous methanol. ^b C. Mannich, *Arch. Pharm.*, **248**, 137 (1910), reports m.p. 48°. ^c Ref. b, m.p. 211°. ^d J. Tambor, *Ber.*, **43**, 188⁺ (1910), reports 44°. ^e *Anal.* Calcd. for C₁₁H₁₅O₃N₃ (237.25); N, 17.71. Found: N, 17.64. ^f F. Unger, *Ann.*, **504**, 267 (1933), reports m.p. 37–38°. ^g Ref. f, m.p. 181.5°. ^h Ref. f, m.p. 29°. ⁱ Ref. f, m.p. 172°; F. v. Wessely, *et al.*, *Monatsh.*, **73**, 127 (1940), give m.p. 175°. ^j R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, **809** (1938), reports m.p. 58–59°. ^k E. Martegiani, *Gazz. chim. ital.*, **42**, II, 348 (1912), reports m.p. 190–192°. ^l L. Gattermann, R. Ehrhardt and H. Maisch, *Ber.*, **23**, 1205 (1890), reports m.p. 30°. ^m *Anal.* Calcd. for C₁₂H₁₇O₃N₃ (235.28); N, 17.46. Found: N, 17.31. The *p*-nitrophenylhydrazones melted at 163–164°. ⁿ *Anal.* Calcd. for C₁₇H₁₉O₃N₃ (314.32); N, 13.37. Found: N, 13.30. ^o P. M. Baranger, *Bull. soc. chim.*, [4] **49**, 1213 (1931), reports m.p. 21–22°. ^p Ref. n, m.p. 183°; ref. f, m.p. 173.5°. ^q *Anal.* Calcd. for C₁₂H₁₆O₃ (208.29); C, 69.21; H, 7.74. Found: C, 69.30; H, 7.55. ^r *Anal.* Calcd. for C₁₃H₁₉O₃N₃ (265.29); N, 15.84. Found: N, 15.63. ^s B.p. 188–190° (40 mm.); A. Sosa, *Ann. chim.*, **14**, 5 (1940), reports b.p. 158.5–159.5° (12 mm.). ^t Ref. r, m.p. 193–194° (heating block) and 206°. ^u S. Skraup and F. Nielsen, *Ber.*, **57**, 1295 (1924), report m.p. 41°. ^v Ref. f, m.p. 142.5°.

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Furfuryl Esters of Some Dicarboxylic Acids

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Earlier authors^{2–7} have prepared furfuryl esters of monocarboxylic acids by a variety of methods, none of which appears to be suitable for the difurfuryl esters of dicarboxylic acids. The reactions of furfuryl alcohol with phthalic and succinic anhydrides give the mono esters. In the present work we found that the difurfuryl esters lacked sufficient volatility and thermal stability to make

(1) From the M.S. thesis of M. J. Mitchell, Louisiana State University, June, 1952.

(2) L. von Wissell and B. Tollens, *Ann.*, **272**, 291 (1893).

(3) J. E. Zanetti, *THIS JOURNAL*, **47**, 536 (1925).

(4) W. R. Edwards, Jr., and L. H. Reeves, *ibid.*, **64**, 1583 (1942).

(5) J. E. Zanetti, *ibid.*, **47**, 1452 (1925).

(6) F. A. Norris and D. E. Terry, *Oil and Soap*, **21**, 193 (1944).

(7) G. Calingaert, H. Soroos, V. Hnizda and H. Shapiro, *THIS JOURNAL*, **62**, 1545 (1940).

TABLE I

Name	Yield, %	M.p. (uncor.), °C.	Carbon, %		Hydrogen, %		Sapn. equiv.	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
Difurfuryl oxalate	58	61.5-62	57.60	57.48	4.03	4.12	125.1	127
Difurfuryl succinate	35	10-12	60.42	60.37	5.07	5.18	139.13	140
Difurfuryl fumarate	39	68-69	60.86	60.79	4.38	4.24	138.12	138
Difurfuryl phthalate	21	130-130.5	66.25	66.18	4.32	4.28	163.14	161
Furfuryl acid succinate	65	8-15	198.2	201
Methyl furfuryl oxalate	23	126.5-127	52.18	51.97	4.36	4.48	92.07	92.5

their preparation by alcoholysis or ester interchange feasible; that the Diels method,⁸ using carbon suboxide, would not give difurfuryl malonate; and that treatment of acetyl succinate monofurfuryl ester with furfuryl alcohol would not yield the succinate.

The reaction of excess sodium furfurylate with acyl halides at low temperatures was found by us to give difurfuryl oxalate, succinate, fumarate and phthalate in yields ranging from 20 to 60%. The malonate and the adipate, the preparations of which were attempted in the same way, could not be isolated. Sodium furfurylate and oxalyl chloride monomethyl ester gave methyl furfuryl oxalate; presumably, other mixed furfuryl esters could be prepared similarly. Furfuryl acid succinate was prepared by the reaction of furfuryl alcohol with succinic anhydride. Esters which were isolated are described in Table I.

In apparent order of diminishing stabilities, these esters may be listed as follows: difurfuryl phthalate, difurfuryl fumarate, furfuryl acid succinate, difurfuryl succinate, difurfuryl oxalate, methyl furfuryl oxalate and difurfuryl malonate. The phthalate was quite stable, while the malonate at the other extreme was so sensitive to heat that the mixture thought to contain it decomposed vigorously on warming to room temperature.

Difurfuryl oxalate (I) decomposed to a black amorphous solid within a few hours when traces of acid or base were present, and within a few days when exposed to atmospheric moisture. When purified by several recrystallizations from carbon tetrachloride and stored in a vacuum desiccator, it showed no apparent change after five days. Saturated ether or carbon tetrachloride solutions, stored in the dark at -10° , were unchanged after four weeks. Addition of a small amount of anhydrous sodium sulfate to these solutions appeared to discourage decomposition; hydroquinone and urea, on the other hand, accelerated it. Pure I decomposed violently at $100-120^{\circ}$ ⁹; less vigorously and at lower temperatures when free oxalic acid was present.

Boiling water hydrolyzed I readily, with 56% loss of ester in one hour. Since furfuryl alcohol is unstable in the presence of oxalic acid, no true hydrolysis equilibrium was achieved, and in time the ester was entirely destroyed. Alcoholysis took place almost as readily. Methoxylation of I with bromine and methanol was accompanied by alcoholysis of the initial material, or the product, or both; methyl oxalate and, presumably, 2,5-dimethoxy-2,5-dihydrofurfuryl alcohol were the chief products, instead of the expected exclusive

(8) O. Diels, R. Beckmann and G. Tonnes, *Ann.*, **439**, 76 (1924).

(9) Cf. reference 4, describing similar behavior, upon heating, of a mixture of oxalic acid and furfuryl acetate.

yield of 2,5-dimethoxy-2,5-dihydrofurfuryl oxalate.

Oxidation of I with neutral aqueous potassium permanganate gave potassium oxalate, among other products, and an unidentified compound thought to be an aldehyde- or keto-acid. No furoic acid could be detected in the reaction products. Since furfuryl alcohol forms furoic acid upon treatment with permanganate, absence of that acid appears to preclude the possibility of an initial hydrolysis of I to the alcohol and the free acid, followed by a preferential oxidation of the alcohol.

Experimental

Sodium Furfurylate.—Sodium metal (0.5 mole) was dispersed by stirring in boiling xylene, which was then siphoned off and replaced by 500 ml. of ether. The flask was placed in an ice-bath, and 49.5 g. (0.505 mole) of freshly-distilled furfuryl alcohol was added dropwise, with stirring; stirring was continued for 36 hours at room temperature. A similar but smaller run gave a yield of 96-97% sodium furfurylate.

Difurfuryl Oxalate (I).—A slurry of 60 g. (0.5 mole) of sodium furfurylate in 500 ml. of dry ether was cooled to -10° . A solution of 25.4 g. (0.2 mole) of freshly-distilled oxalyl chloride in 250 ml. of dry ether was added dropwise with rapid stirring over a four-hour period, the temperature being kept below 5° . The mixture was filtered with suction, and the residue washed ten times with 50-ml. portions of ether which were added to the filtrate. The latter was shaken with 5% aqueous sodium bicarbonate, and dried over sodium sulfate, the ether removed by vacuum at 25° , and the residue placed in an ice-water-bath for 30 minutes. The white crystals of I which formed were recrystallized once from carbon tetrachloride, and dried in a vacuum desiccator. They were very soluble in ether, acetone and benzene, approximately 12% soluble in carbon tetrachloride, and 0.4% soluble in water, at 25° . Best results were obtained when separation and purification of I were carried out as rapidly as possible, attendant impurities apparently possessing a marked ability to promote its decomposition.

Other Difurfuryl Esters.—Preparations of the fumarate, the succinate and the phthalate were essentially similar to that of I. In the case of the succinate, the dried ethereal solution of the ester was concentrated to 25 ml. at 25° under reduced pressure, and cooled to -85° . The ester precipitated as a hard amorphous solid, which decomposed at 90° , and could not be distilled at 5 mm.

An attempt to prepare the adipate by a method similar to that used for I produced a light yellow oil which failed to deposit crystals at -78° . Distillation at 1.5 mm. gave a few drops of a product which decomposed rapidly on exposure to air; the remainder charred in the distilling flask. A similar attempt to prepare the malonate gave a product from which no crystals were obtained on standing at -20° , and which decomposed almost violently on warming to room temperature, with formation of a quantity of gas and a hard black resin.

Attempted Preparations by Other Methods. (a) (I) **By Alcoholysis.**—Methyl oxalate was prepared by Bowden's method,¹⁰ and recrystallized from hot methanol containing sodium carbonate, anhydrous sodium sulfate and charcoal; this modified purification gave a 75% yield of acid-free crystals, m.p. $52-53^{\circ}$. A mixture of methyl oxalate, excess furfuryl alcohol, benzene and a trace of sodium furfurylate was heated at 60° for one hour, but no evidence of methanol formation could be obtained. At 82° (19 mm.) a little more

(10) E. Bowden, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 414.

than half of the original furfuryl alcohol distilled, leaving a black tarry residue from which no identifiable products could be extracted.

(b) (I) **By Ester Interchange.**—Employing the method of Calingaert, *et al.*,⁷ furfuryl acetate, methyl oxalate and a trace of freshly-sublimed aluminum ethoxide were heated together at 50° for five hours, and distilled under reduced pressure. Products included small amounts of the original reactants, and a black tar from which no I could be extracted.

(c) **Difurfuryl Malonate, by the Diels Method.**—Carbon suboxide, prepared from malonic acid and phosphorus pentoxide, was treated with excess furfuryl alcohol. The clear solution was kept at -70° for 5 hours, gradually turning brown. On warming to room temperature the solution effervesced and turned black. The residue charred on heating, and distillation at 5 mm. produced no ester.

(d) **Difurfuryl Succinate from Acetyl Succinate Monofurfuryl Ester.**—A solution of furfuryl acid succinate in ether was treated with ketene at -10° to form acetyl succinate monofurfuryl ether. This was treated with furfuryl alcohol at the same temperature, but no difurfuryl succinate was obtained. Distillation at 5.8 mm. yielded a trace of furfuryl acetate and a black intractable tar.

Furfuryl Acid Succinate.—Using a procedure similar to that of Adams and Gauerke¹¹ for furfuryl acetate, 51 g. (0.52 mole) of furfuryl alcohol was heated with 50 g. (0.5 mole) of succinic anhydride and 40.5 g. of anhydrous sodium succinate. The product, a liquid which could not be distilled at 5 mm., was dissolved in aqueous sodium hydroxide, decolorized with charcoal, and precipitated with 10% hydrochloric acid. It was believed to be furfuryl acid succinate. No difurfuryl succinate was detected.

Methyl Furfuryl Oxalate.—Oxalyl chloride monomethyl ester was prepared by the method of von Frank and Caro.¹² The portion boiling at 118-120° (757 mm.) was added to sodium furfurylate, following the procedure employed for the preparation of I.

Oxidation of I.—A neutral solution of 15.8 g. (0.05 mole) of potassium permanganate in 200 ml. of water was added dropwise with stirring to a solution of 6.25 g. (0.025 mole) of I in 100 ml. of ether at 5°. Manganese dioxide was removed by filtration, and the ether and water layers were separated. Evaporation of the ether led to recovery of 2.8 g. of unreacted I. The aqueous layer was concentrated to 85 ml. on the steam-bath and treated with 10% lead acetate solution; 2.03 g. of lead oxalate precipitated.

The aqueous filtrate, after separation of the lead oxalate, was evaporated to dryness at 25°, yielding 1.48 g. of a crystalline compound which decomposed slowly when exposed to air. It gave a positive test for potassium with sodium cobaltinitrite, and when treated with phenylhydrazine formed a solid which decomposed without melting at 200-250°. Tentatively, it was regarded as the potassium salt of an aldehyde- or keto-acid. Attempts to secure the free acid by treatment with mineral acids led to decomposition.

Treatment of I in methanol with 4% hydrogen peroxide and a trace of ferrous sulfate for 24 hours at 0° resulted in complete destruction of the ester. No identifiable products could be isolated.

Methoxylation of I.—A mixture of 12.5 g. (0.05 mole) of I, 150 ml. of methanol and 20 g. of potassium acetate was cooled to -10°, and a cold solution of 8 g. (0.1 mole) of bromine in 50 ml. of methyl alcohol was added dropwise with stirring. Sodium bromide was removed by filtration, and the filtrate concentrated to 15 ml., precipitating 3.2 g. of methyl oxalate. The supernatant liquid, which presumably contained 2,5-dimethoxy-2,5-dihydrofurfuryl alcohol and perhaps some 2,5-dimethoxy-2,5-dihydrofurfuryl oxalate, was hydrolyzed and treated with 5 ml. (0.1 mole) of hydrazine hydrate, following the procedure of Clauson-Kaas and Limborg.¹³ This gave 0.98 g. of 3-hydroxymethylpyridazine, identified by mixed melting point with a sample prepared from furfuryl acetate.

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(11) R. Adams and C. G. Gauerke, "Organic Syntheses," Coll. Vol. I, 2nd Edition, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 285.

(12) G. von Frank and W. Caro, *Ber.*, **63**, 1532 (1930).

(13) N. Clauson-Kaas and F. Limborg, *Acta Chem. Scand.*, **1**, 619 (1947).

Degradation of Isotopically-labeled Glucose via Periodate Oxidation of Gluconate¹

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Radioactive tracer studies currently in progress in this Laboratory have required a method for assaying the radioactivity in the terminal carbon atoms of biosynthetic glucose. Gluconic acid suggested itself as a derivative of glucose suitable for degradation inasmuch as periodate oxidation of gluconate should yield both carbon-1 and carbon-6 separately from a single sample. To test this method, glucose, variously labeled with C¹⁴, was oxidized to potassium gluconate in high yield and purity by the procedure of Moore and Link³; the gluconate was then oxidized with periodate with the expectation of obtaining CO₂ from C-1, HCOOH from C-2,3,4,5, and HCHO from C-6.

In the first attempts to evaluate this method periodic acid at pH 1 was selected as the oxidant. H₅IO₆ was added to a solution of potassium gluconate in the ratio of six moles of oxidant to one of gluconate, and the consumption of periodate was followed by the iodometric procedure of Jackson.⁴ It can be seen from Fig. 1 that the oxidation proceeds rapidly until four moles are consumed and then slowly approaches the theoretical consumption of five moles after about 20 hours. The yield of CO₂, collected as BaCO₃ during the first two hours, was only 50% of theoretical, a fact which suggests that the bond between carbons 1 and 2 is the last to be split. When the method was tested with gluconate-1-C¹⁴, the specific activity in C¹⁴O₂ evolved during the same two hour period was only 80% of that in C-1 of the gluconate (Table I). Apparently CO₂ is coming from some other source as well as from C-1. In spite of the theoretical stoichiometry observed, the method is unsatisfactory for the allocation of isotope in labeled gluconate.

Some further experiments have been performed in an attempt to reveal the source of the extraneous CO₂ and possibly to suggest a mechanism to explain these results. Any mechanism must take into account the theoretical uptake of H₅IO₆; further oxidation of the fragments by H₅IO₆ is therefore ruled out unless the "theoretical" value observed is fortuitous. To test the possibility that HIO₃ (a product of the periodate oxidation) might oxidize the split products, a system was set up containing H₅IO₆, HIO₃, HCOOK and HCHO. No CO₂ was evolved over a period of three hours. Hence the preformed split products are not susceptible to further oxidation either by H₅IO₆ or HIO₃.

Gluconate-2-C¹⁴ and gluconate-6-C¹⁴ have both been subjected to periodate oxidation at pH 1 (Table I). Whereas no C¹⁴O₂ was generated from gluconate-6-C¹⁴, C¹⁴O₂ was a product of oxidation of gluconate-2-C¹⁴ and accounted for some 2% of

(1) This investigation was supported in part by a research grant A-324, from the National Institute of Arthritis and Metabolic Diseases, of the National Institutes of Health, Public Health Service.

(2) National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

(3) S. Moore and K. P. Link, *J. Biol. Chem.*, **133**, 293 (1940).

(4) E. L. Jackson, "Organic Reactions," Vol. 11, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 361.