with neutral potassium permanganate, and elementary analysis showed the presence of sulfur. A small sample on heating above the melting point gave off sulfur dioxide to produce a liquid, b.p. 292°. A portion of this liquid was saponified with alcoholic sodium hydroxide for 2 hours, acidified with concentrated hydrochloric acid, evaporated to dryness, and sublimed under a vacuum of 6 mm. to give long white needles of phthalic anhydride (XI), m.p. 127–129° (sealed tube). A mixed melting point (sealed tube) with an authentic sample of phthalic anhydride (XI) showed no depression.

**Fluorene (XV).**—To the chloroform extract, dried over magnesium sulfate, resulting from the decomposition of 20 g. (0.066 mole) of 3-dimethylamino-2,3-dihydrothiophene 1-dioxide methiodide and assumed to contain 5.06 g. (0.0436 mole) of thiophene-1-dioxide (I) (based on the reaction with dimethylamine) was added 5.04 g. (0.00436 mole) of freshly distilled indene (b.p. 74–75°/(20 mm.)) and a trace of N-phenyl-β-naphthylamine. The resulting solution was allowed to stand in a well-stoppered flask for 87 hours at room temperature. A yellow solution was obtained which contained a small amount of viscous insoluble oil. The resulting mixture was boiled under reflux for 2 hours, cooled and separated from the insoluble oil. The chloroform solution was evaporated on the steam-bath at atmospheric pressure to a volume of about 75 ml. An additional amount of insoluble oil which formed during the evaporation was separated. The resulting chloroform solution was evaporated to dryness, under vacuum, at room temperature to give 10.96 g. of a red oil containing a small amount of solid.

Extraction of this oil with petroleum ether and distillation of the soluble fraction yielded unreacted indene. The semisolid residue in the distillation flask and column after recrystallization from an ethanol–water mixture gave 0.2 g. (3%) pure white plates of fluorene (XV), m.p. 109–110°. There was no depression in melting point when XV was mixed with an authentic sample of fluorene (XV).

COLLEGE PARK, MARYLAND

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE]

# 2-Pyrones. IX. 2-Pyrone-6-carboxylic Acid and its Derivatives

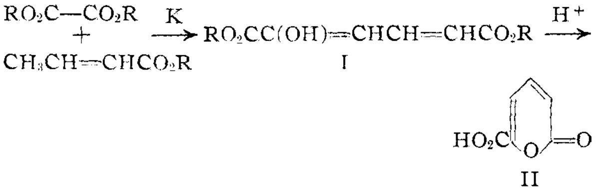
BY RICHARD H. WILEY AND ALBERT J. HART

RECEIVED NOVEMBER 23, 1953

2-Pyrone-6-carboxylic acid (II), a key intermediate in 2-pyrone chemistry, has been obtained in 30.7% yields by an improved process and converted to eighteen new derivatives including the chloride, amide and several alkyl, aryl, and glycol esters. Diethyl 2,4-hexadiene-5-hydroxy-1,6-dioate (I), obtained from diethyl oxalate and ethyl crotonate in 48–63% yields by using potassium in toluene for the condensation, has been converted to 2-pyrone-6-carboxylic acid in 50% yield by hydrolysis and lactonization.

A thorough reinvestigation of methods for the preparation of 2-pyrone in our laboratories has confirmed previous reports[1] that decarboxylation of 2-pyrone-6-carboxylic acid (II) is by far the most practical preparation. The decarboxylation of coumalic acid, the 5-carboxy isomer, appears to be of no preparative value whatever although it is frequently mentioned in texts. Unfortunately, the preparation and properties of 2-pyrone-6-carboxylic acid have not been studied in any detail so that this route to 2-pyrone remains obscure. The present paper presents the results of our study of the preparation of this acid and its conversion to a variety of derivatives for evaluation as possible inhibitors of tumor growth.

2-Pyrone-6-carboxylic acid was first prepared[2] by cyclization of the condensation product obtained from diethyl oxalate and ethyl crotonate. The



$$\begin{matrix} RO_2C{-}CO_2R \\ + \\ CH_3CH{=}CHCO_2R \end{matrix} \xrightarrow{K} \underset{\text{I}}{RO_2CC(OH){=}CHCH{=}CHCO_2R} \xrightarrow{H^+} \text{II}$$

condensation was stated to give up to 40% yield with sodium or sodium ethoxide in ether or toluene as catalyst. Similar yields have also been reported[3] using sodium metal in petroleum ether for the condensation. It also has been reported[4] that ethyl vinylacetate can be used in place of ethyl crotonate but this offers no apparent advantages. In the preparation of a series of related compounds from higher homologs of crotonic ester it has been noted[1] that potassium ethoxide is superior to sodium ethoxide for condensations of this type. None of these previous studies reported conditions for this condensation which we found to be reproducible and the only reactions studied have been the decarboxylation,[1] relative resistance to ammonolysis of the ring,[1] and formation of the ethyl ester.[2]

Our studies have consistently shown that the condensation of diethyl oxalate and ethyl crotonate with sodium, sodium methoxide or sodium ethoxide either fails completely or gives less than 10% of product. With potassium ethoxide we have obtained reproducible yields of 36–46% in the condensation. The search for a reagent more convenient to use than the potassium ethoxide has shown that 48–63% of the condensation product can be obtained using potassium metal in toluene and a convenient procedure, uniformly reproducible in our hands, based on use of this reagent is described in the experimental section. In the course of our development of this procedure we have observed the effect of changing several variables on the yield obtained. The yield is still within the range of 48–63% when a slight excess of any one of the three reactants—potassium, ethyl oxalate or ethyl crotonate—is used; when a trace of potassium chloride or ethanol is added; and when the time for precipitation of the potassium salt is lengthened. The yield is definitely decreased if the methyl esters are used; if the ethyl crotonate is added immediately after addition of the ethyl oxalate to the

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(1) J. Fried and R. C. Elderfield, *J. Org. Chem.*, **6**, 566 (1941).

(2) A. Lapworth, *J. Chem. Soc.*, **79**, 1279 (1901).

(3) B. Prager, *Ann.*, **338**, 375 (1905).

(4) A. B. Boese and R. T. Major, THIS JOURNAL, **56**, 949 (1934).

TABLE I

ESTERS OF 2-PYRONE-6-CARBOXYLIC ACID

| Ester | M.p., °C. | Solvent[a] | Yield, % | Analyses,[b] % | | | |
|---|---|---|---|---|---|---|---|
| | | | | Carbon | | Hydrogen | |
| | | | | Calcd. | Found | Calcd. | Found |
| Methyl | 124–125 | B | 98 | 54.56 | 54.54 | 3.93 | 3.95 |
| Isobutyl | 100–102 | A | 73 | 61.20 | 61.22 | 6.17 | 6.42 |
| *n*-Amyl | 56–58 | P | 73 | 62.85 | 62.99 | 6.71 | 6.85 |
| Dodecyl | 67–68 | A | 87 | 70.10 | 70.60 | 9.15 | 9.26 |
| Cyclohexyl | 108–109 | A | 68 | 64.85 | 64.96 | 6.35 | 6.62 |
| Pentaerythrityl | 218–221 | S | 40 | 55.78 | 55.80 | 3.23 | 3.35 |
| Ethylene glycol | 231–232 | D | 29 | 54.90 | 54.65 | 3.29 | 3.73 |
| Trimethylene glycol | 140–142 | E | 92 | 56.28 | 56.42 | 3.78 | 3.93 |
| Pentamethylene glycol | 123–125 | T | 69 | 58.62 | 58.78 | 4.63 | 4.82 |
| Decamethylene glycol | 146–148 | T | 70 | 63.15 | 63.22 | 6.26 | 6.12 |
| Diethylene glycol | 137–138 | T | 62 | 54.85 | 54.76 | 4.03 | 4.05 |
| Thiodiethylene glycol | 125–128 | T | 23 | 52.46 | 52.58 | 3.85 | 3.90 |
| Triethylene glycol | 104–105[c] | B | 81 | 54.84 | 54.92 | 4.60 | 4.88 |
| Phenyl | 127–128 | B, P | 82 | 66.65 | 66.76 | 3.73 | 3.90 |
| *p*-Methoxyphenyl | 140–142 | C | 67 | 63.40 | 63.52 | 4.09 | 4.40 |
| 2,6-Dimethoxyphenyl | 151–152 | E | 25 | 60.87 | 60.73 | 4.38 | 4.46 |

[a] The solvent used in recrystallization is indicated by B, benzene; A, aqueous alcohol; P, petroleum ether; S, acetic acid; D, dioxane; E, ethanol; T, toluene; C, acetone–water. [b] Analyses by Micro-Tech Laboratories, Skokie, Illinois. [c] Softens at 97°.

reaction mixture; or if petroleum ether is used as reaction medium. The use of potassium ethoxide or ether as the reaction medium is much less convenient and gives slightly lower yields.

The cyclization of the diethyl 2,4-hexadiene-5-hydroxy-1,6-dioate (I) to 2-pyrone-6-carboxylic acid involves acid hydrolysis of the ester and spontaneous lactonization. Isolation of the product by evaporation of the reaction mixture as previously described[2] is less successful than proper selection of conditions such that the acid can be precipitated by cooling the reaction mixture. There is no advantage in using either hydrochloric acid or hydrobromic acid in glacial acetic acid for the reaction. The preferred conditions described in the experimental section give approximately 50% yields for this step in the reaction.

For the purpose of further characterizing 2-pyrone-6-carboxylic acid and to provide compounds structurally related to other unsaturated lactones known to inhibit the growth of tumors we have synthesized and characterized the acid chloride, the amide and several alkyl, aryl and bis esters. The fact that the amide can be obtained in good yields is consistent with the observation[2] that the pyrone ring is relatively stable toward ammonolysis to the pyridone. In other studies, we have, however, converted this acid to pyridones in good yields. There is no question that the product is the amide, m.p. 200–203°, and not the previously reported 2-pyridone-6-carboxylic acid, m.p. 280°.[1] The phenyl esters are believed to be esters—not keto-phenolic compounds formed by an acylation reaction—because they show no phenolic behavior. Apparently even at the high temperatures at which these compounds were prepared no Fries rearrangement has taken place.

**Acknowledgment.**—The authors acknowledge with appreciation a grant from the Damyon Runyon Fund which made this study possible.

## Experimental

**2-Pyrone-6-carboxylic Acid.**—To 500 ml. of dry toluene in a flask protected from atmospheric moisture were added 19.5 g. (0.499 mole) of finely-cut potassium and 73.0 g. (0.500 mole) of freshly distilled diethyl oxalate (E. K. Co.). After two hours, 57.0 g. (0.500 mole) of freshly distilled ethyl crotonate was added. The reaction flask was cooled in a water-bath to control an exothermic reaction which began within 45 minutes with the formation of a yellow precipitate of the potassium salt of diethyl 2,4-hexadiene-5-hydroxy-1,6-dioate. After ten hours the precipitate was collected, washed thoroughly with petroleum ether, and dried over paraffin. The potassium salt was dissolved in 1 l. of water to which 75 ml. of concd. hydrochloric acid was added. After cooling, the precipitated, solid diethyl 2,4-hexadiene-5-hydroxy-1,6-dioate was collected and washed with water.

The crude ester was heated with 90 ml. of concd. hydrochloric acid for six hours in a water-bath at 100°. After cooling, the crude pyrone acid was collected. The filtrate was evaporated to 25 ml. and cooled to precipitate an additional quantity of the acid. The combined precipitates of crude acid were recrystallized from 100–125 ml. of hot water, treated hot with Norit, filtered, and cooled to reprecipitate 19.3 g. (27.6% of the theoretical amount) of dry 2-pyrone-6-carboxylic acid, m.p. 228–230°. An additional 2.2 g. was obtained on concentration of the mother liquors to give a total yield of 30.7% of the theoretical amount.

**2-Pyrone-6-carbonyl Chloride.**—To 45.0 g. (0.322 mole) of 2-pyrone-6-carboxylic acid in a 125-ml. Claisen flask was added 90 ml. (1.25 moles) of thionyl chloride. The mixture was heated under reflux at 100° for 14 hours to dissolve the acid. The excess thionyl chloride was removed under vacuum and the residue distilled from the reaction flask to give 47.8 g. (93.8% of the theoretical amount) of 2-pyrone-6-carbonyl chloride, b.p. 160–161° (18 mm.), 177–178° (30 mm.), 182–183° (40 mm.), m.p. 72–73°.

*Anal.* Calcd. for $C_6H_3O_3Cl$: Cl, 22.37. Found: Cl, 22.18.

**2-Pyrone-6-carboxamide.**—This amide was prepared by saturating a solution of 5.0 g. (0.032 mole) of 2-pyrone-6-carbonyl chloride in 150 ml. of dry ether with dry ammonia. The precipitate was collected, washed with 10 ml. of water, and recrystallized from hot water to give 1.8 g. (41% of the theoretical amount) of 2-pyrone-6-carboxamide, white needles, m.p. 200–203°. The amide was also prepared, but in lower yield, by adding cold, concentrated ammonium hydroxide to the acid chloride.

*Anal.* Calcd. for $C_6H_5O_3N$: N, 10.07. Found: N, 10.10.

**Ethyl 2-pyrone-6-carboxylate** was prepared by heating 2-pyrone-6-carbonyl chloride with a large excess of absolute ethanol. The ethanol was removed under reduced pressure to leave a residue which on recrystallization from ligroin gave ethyl 2-pyrone-6-carboxylate, plates, m.p. 59–61°, reported[2] m.p. 59–60°.

**Methyl 2-Pyrone-6-carboxylate.**—This ester was prepared by adding 25.0 g. (0.157 mole) of 2-pyrone-6-carbonyl chloride to 100 ml. (0.248 mole) of dry methanol. After the initial vigorous reaction, the reaction mixture was refluxed 15 minutes. The excess methanol was evaporated and the residue recrystallized from benzene to give 23.7 g. (98% of the theoretical amount) of methyl 2-pyrone-6-carboxylate, rectangular plates, m.p. 124–125°. Analytical data are given in Table I.

**Cyclohexyl 2-Pyrone-6-carboxylate.**—This ester was prepared by heating 5.0 g. (0.032 mole) of 2-pyrone-6-carbonyl chloride with 3.2 g. (0.032 mole) of cyclohexanol at 100° for one-half an hour. The solid which formed on cooling the reaction mixture was recrystallized from ethanol–water to give 4.8 g. (48% of the theoretical amount) of cyclohexyl 2-pyrone-6-carboxylate, white needles, m.p. 108–109°. Analytical data are given in Table I.

**Isobutyl, *n*-amyl and dodecyl 2-pyrone-6-carboxylates** were prepared by the same procedure used for the preparation of the cyclohexyl ester. Yields, properties and analytical data are given in Table I.

**Pentaerythrityl Tetrakis-(2-pyrone-6-carboxylate).**—This ester was prepared by heating a mixture of 3.5 g. (0.022 mole) of 2-pyrone-6-carbonyl chloride and 0.75 g. (0.0055 mole) of powdered pentaerythritol at 150° to the solution. The solid which formed on cooling was recrystallized from hot acetic acid and dried to give 1.4 g. (40% of the theoretical amount) of white crystals of pentaerythrityl tetrakis-(2-pyrone-6-carboxylate), m.p. 218–221°. Analytical data are given in Table I.

**Decamethylene Glycol Bis-(2-pyrone-6-carboxylate).**—This ester was prepared by heating 5.0 g. (0.032 mole) of 2-pyrone-6-carbonyl chloride with 2.8 g. (0.016 mole) of 1,10-decanediol (decamethylene glycol) at 100° for one-half hour. The solid which formed on cooling was triturated with 50 ml. of ethanol, collected on a filter, and recrystallized from toluene to give 4.6 g. (70% of the theoretical amount) of 1,10-decanediol bis-(2-pyrone-6-carboxylate), m.p. 146–148°. Analytical data are given in Table I.

**Ethylene glycol, trimethylene glycol,[5] pentamethylene glycol, diethylene glycol[5] and triethylene glycol[5]** bis esters of 2-pyrone-6-carboxylic acid were prepared by the same procedure used for the preparation of the 1,10-decanediol bis ester. Analytical and yield data are given in Table I.

***p*-Methoxyphenyl 2-Pyrone-6-carboxylate.**—A mixture of 5.0 g. (0.032 mole) of 2-pyrone-6-carbonyl chloride and 4.0 g. (0.032 mole) of *p*-methoxyphenol was heated slowly to 150° and held at 150–160° for five hours. The solid that formed on cooling the reaction mixture was recrystallized from acetone–water to give 5.2 g. (67% of the theoretical amount) of *p*-methoxyphenyl 2-pyrone-6-carboxylate, m.p. 140–142° (after several recrystallizations). Analytical data are given in Table I.

**Phenyl and 2,6-dimethoxyphenyl 2-pyrone-6-carboxylate** were prepared by the procedure given for the preparation of the *p*-methoxyphenyl ester. The 2,6-dimethoxyphenyl ester was prepared by heating the reactants at 180–190° for one hour. Analytical data are given in Table I.

None of the aryl esters gave positive ferric chloride enol tests or were readily soluble in cold, dilute sodium hydroxide.

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[5] The authors wish to thank Carbide and Carbon Chemicals Corporation for generously providing samples of these glycols.

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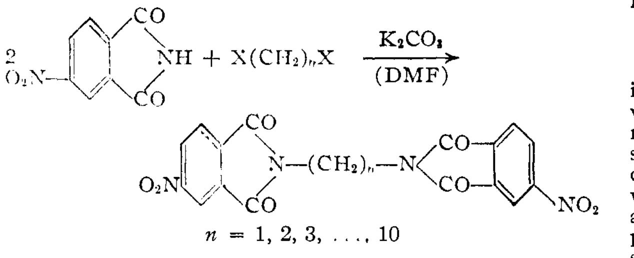
# NOTES

## 4-Nitrophthalimide. II. Di-(4-nitrophthalimido)-alkanes and Bis-(4-nitrophthalimidoalkyl) Ethers[1]

BY JOHN H. BILLMAN AND R. VINCENT CASH

RECEIVED NOVEMBER 27, 1953

In a previous article[2] it was shown that N-alkyl-4-nitrophthalimides may be prepared by the reaction of 4-nitrophthalimide and potassium carbonate with the corresponding monohaloalkane in a medium of dimethylformamide. It seemed a logical extension of this work to attempt the preparation of a number of $\alpha,\omega$-di-(4-nitrophthalimido)-alkanes from dihaloalkanes with terminal halogen atoms.



In order to minimize the formation of N-(bromoalkyl)-4-nitrophthalimides, a ratio of 1:2.5 moles of the dibromide to the 4-nitrophthalimide was used in preparing the series of di-(4-nitrophthalimido)-alkanes (Table I) having one to ten (except eight) carbon atoms in the normal hydrocarbon chain. Bis-(4-nitrophthalimido)-ethyl ether and bis-(4-nitrophthalimido)-isopropyl ether (Table I) were obtained from the corresponding chloro ethers by a similar procedure. It should be noted that a longer period of heating of the reaction mixture gave higher yields.

The melting points of these di-(4-nitrophthalimido)-alkanes are of particular interest in that they follow the "sawtooth" effect with the compounds containing an even number of carbon atoms, in the chain, melting at a higher temperature than the next higher and lower homolog.

### Experimental

**Di-(4-nitrophthalimido)-alkanes and Bis-(4-nitrophthalimidoalkyl) Ethers.**—In a 250-ml. round-bottomed flask with thermometer well were placed 9.6 g. (0.050 mole) of 4-nitrophthalimide, 4.2 g. (0.030 mole) of anhydrous potassium carbonate and 0.2 g. of potassium iodide. The dried dihalide (0.020 mole) and 40 ml. of dimethylformamide were added and a reflux condenser bearing a drying tube was attached. The mixture was heated at 135–140° for the period indicated in Table I. The flask was shaken occasionally. Carbon dioxide was evolved during the heating period.

The reaction mixture became solid on cooling to room temperature. It was introduced into 200 ml. of cold water, and the solid permitted to settle. After collecting the solid, it was washed with two 25-ml. portions of 2% sodium hydroxide, and finally with water. The dried crude product was recrystallized by dissolving it in a minimal volume of hot chloroform, filtering while hot, and then adding 95%

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[1] Contribution from the Chemistry Departments of Indiana University (No. 613) and Teachers College of Connecticut.

[2] J. H. Billman and R. V. Cash, THIS JOURNAL, **75**, 2499 (1953).