Reaction of Pyromeconic Acid with β-Diazopropionic Ester. Synthesis and Attempted Cyclization of β-(4*H*-Pyran-4-on-3-yloxy)propionic Acid

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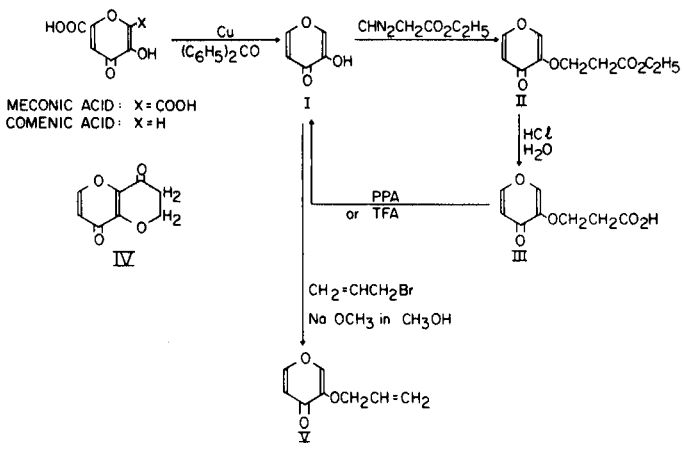
A procedure which utilizes a special sublimate condenser for preparation of pyromeconic acid (I) by decarboxylation of either meconic or comenic acid is reported. *O*-Alkylation of pyromeconic acid with ethyl β-diazopropionate *ex situ* yields ethyl β-(4*H*-pyran-4-on-3-yloxy)-propionate (II), acidic hydrolysis of which affords the free acid III. The acid III is refractory to ring-closure to a chromanone analog IV under a wide range of acidic conditions. *O*-Allylation of I gives 3-allyloxy-4*H*-pyran-4-one (V) as a low-melting crystalline solid.

The preparation of pyromeconic acid (I) by decarboxylation of either comenic (1) or meconic acid (2) has been reported by several workers, among them Robiquet and Stenhouse who described I over 100 years ago. The decarboxylation requires rather high temperatures, which result in a vigorous reaction and rapid evolution of large quantities of carbon dioxide, especially if meconic acid is the reactant. In large scale preparations, gaseous carbon dioxide sweeps out the product pyromeconic acid sublimate in all conventional sublimation apparati studied by us, with attendant large losses in yield. In order to minimize such losses, a special sublimate condenser (Experimental) has been designed, which permits effective trapping of the pyromeconic acid sublimate. The special sublimate condenser is a long Vigreux column, surrounded by a large glass cooling jacket. In view of the availability of kojic acid, it is convenient to employ comenic acid as the reactant, obtained by catalytic oxidation of kojic acid (3).

CHART I



O-Alkylation of pyromeconic acid is effected with ethyl β-diazopropionate, prepared *ex situ*, as previously described (5). As with kojic acid (5), it is essential to add I in the solid state in order to obtain a reaction, which proceeds with vigorous nitrogen evolution. The product ethyl β-(4*H*-pyran-4-on-3-yloxy)propionate (II) is obtained initially as an oil which crystallizes readily only after chromatographic purification. In subsequent preparations, nucleation with crystalline II obviated the chromatography step. The structure assigned is supported by combustion analysis, infrared and nmr spectra, and a negative ferric chloride test.

A short-term hydrolysis of II in dilute aqueous hydrochloric acid at 60° gave a good yield of β-(4*H*-pyran-4-on-3-yloxy)propionic acid (III). Combustion analysis supported the structure, as well as the solid state infrared spectrum, in which carboxyl and pyrone carbonyl stretching bands appeared at 1745 and 1665 cm^{-1} respectively. The acid was insufficiently soluble to permit an nmr spectrum.

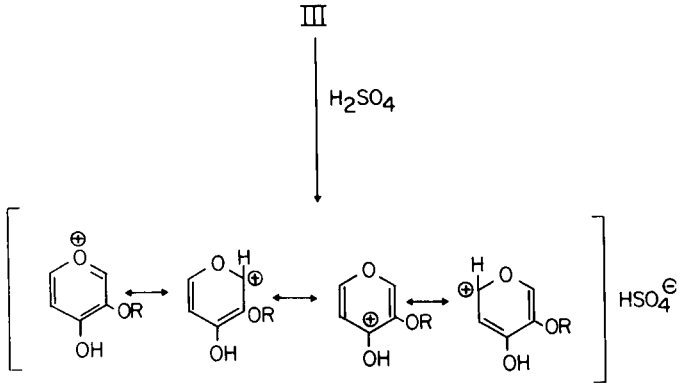
With the acid III in hand, investigation of synthesis of the chromanone analog IV *via* intromolecular cyclization became possible. The following reagents were employed: polyphosphoric acid (PPA) (4), sulfuric acid (concentrated and 80%), boron trifluoride-acetic acid complex (6), phosphorus pentoxide in benzene (7), phosphoryl chloride-zinc chloride, trifluoroacetic anhydride (TFAA) (8), and trifluoroacetic acid (TFA) (9). In addition, thionyl chloride was employed to give the crude acid chloride, with subsequent attempted cyclization by aluminum chloride (7). In no instance was IV obtained. Because equipment for safely handling anhydrous liquid hydrogen fluoride (7) was unavailable, no study of this substance was attempted.

In view of the known utility of PPA in preparing chromanones from the appropriate acid (4,5), this reagent was given detailed attention. Although the test of Uhlig (10) indicated that a reaction probably would take place, no product proved isolable at room temperature. Temperatures then were varied from that of the room to 180°, and reaction periods from two to twenty hours. The desired product never was obtained. Small quantities of (I) resulted, indicating the lability of the exocyclic oxide bond under the reaction conditions. Sulfuric acid and TFA also caused ether cleavage, leading to (I). With the exception of TFAA (sequel) and the Friedel Crafts reaction, unchanged acid was recovered. The latter reaction gave an intractable red oil.

Nmr spectral evidence was obtained that III very probably reacted with TFAA to give a mixed anhydride. Thus during reaction mixture workup, when methanol was added to a residual oil, there was obtained a crystalline product which almost certainly was methyl β-(4*H*-pyran-4-on-3-yloxy)propionate. The nmr spectrum is in accord with the assigned structure. Presumably a mixed anhydride of III with TFA formed, but it was no more reactive than the acid chloride or the free acid in cyclizing.

The negative results in the attempted ring-closure of III must be interpreted with caution, since conceivably IV may have been formed in very low yield. Nonetheless, it is evident that ring-closure of III certainly is not facile under acidic conditions. Whether III is considered to be an α,β-unsaturated ketone, or a pyrylium salt (Scheme I), the overall effects are similar; namely, $C_{(2)}$ acquires considerable electropositive character, and resists attack by the carbonyl-carbon atom of acid or acid chloride. In a previous study (5) of five β-aryloxypropionic acids, only β-(6-bromo-2-naphthoxy)propionic acid was cyclized to the chromanone derivative in polyphosphoric acid, and then in low yield. An electron-withdrawing nitro group on the benzene ring prevented ring-closure.

SCHEME I



In a projected alternate approach to IV, the allyl ether (V) of I was prepared. Although the allyl ether previously has been reported as an oil (11), we obtained V as a low-melting solid. Our findings are in reasonable agreement with the previous ones (11) about the properties of 2-allyl-3-hydroxy-4*H*-pyran-4-one (VI), obtained by Claisen rearrangement of V. The present nmr data confirm that the allyl group is indeed in both the V and VI molecules, and that a rearrangement to the propenyl derivative, known to be facile with 2-allyl-γ-pyrone derivatives (11,12,13), did not occur. Oxidation experiments with VI, in which selenium dioxide and a catalytic air-oxidation procedure were used, did not give useful results. With selenium dioxide a reaction occurred, but no organic product proved isolable. Catalytic air-oxidation (3) gave an unidentified substance which underwent decarboxylation to (I) during attempted isolation.

EXPERIMENTAL (14)

Pyromeconic Acid.

Decarboxylation of comenic or meconic acid was used to prepare pyromeconic acid. In order to minimize losses of the latter through sweeping by product gaseous carbon dioxide, a special sublimate condenser (SSC) was designed. Essentially the SSC was a Vigreux column surrounded by a large cooling jacket. The inner Vigreux column was of total length 79 cm., of which 46 cm. was of outside diameter 2.5 cm., and the remainder of outside diameter 4.0 cm. The outside diameter of the cooling jacket was 9.5 cm. The cooling jacket was open at the top near the small bore end of the inner column to permit introduction of coolant, and was fitted near the large bore end of the inner column with a stopcock to permit convenient egress of coolant at the end of the decarboxylation. The inner Vigreux column was permanently attached by glass seals to the cooling jacket, and also was permanently attached through seals at the small bore end with a straight g.g. male 24/40 joint, and at the large bore end with a similar 24/40 joint, bent downward at a 45° angle to the horizontal.

A three-necked flask was charged with 50 g. copper powder, 110 g. benzophenone, and 50 g. of meconic acid, all of which had previously been dried *in vacuo* over phosphorus pentoxide for 24 hours. The reaction flask was equipped with a g.g. stirring assembly in the central neck, and with a gas inlet tube in one of the side necks. The SSC was attached, at the large bore end, to the other neck. A 250-watt infrared lamp, or electrical heating tape, was used to heat the side arm leading to the SSC to prevent plugging by subliming pyromeconic acid. The remote end of the SSC was fitted with a 500-ml. two-necked flask (dry ice trap: DIT) which was filled with dry ice in such a way that the flow of gaseous carbon dioxide and pyromeconic acid would not be impeded. A stopper bearing a glass tube, which projected into a cylinder (C) containing 100 ml. methanol, was placed in the second neck of the DIT. The cooling jacket of the SSC was filled with acetone and cooled with dry ice until the latter could be added with no appreciable evolution of gas. Stirring was started and the side arm leading into the SSC was heated by an infrared lamp. Dry nitrogen was passed over the reactants for about five minutes before the reaction flask was heated. The reaction flask then was heated in a mantle for about 3 hours at 220°, with nitrogen

passing continually over the decarboxylation mixture. Dry ice was added to the cooling jacket during the reaction as needed to maintain as cold a coolant temperature as possible. The methanol in (C) was monitored carefully for cessation of gas evolution as an indication of possible plugging and subsequent pressure build-up in the decarboxylation apparatus.

Product pyromeconic acid solidified in the SSC, and some product also was collected in the DIT and in the methanol in (C). The product was washed from the SSC and DIT with hot methanol. The washings were combined with the methanol in (C), and solvent removed under reduced pressure. The brown residual solid was dissolved in boiling 1,2-dichloropropane and charcoal added. After boiling for a few minutes, filtration (Celite mat) gave a virtually colorless solution from which there separated white needles of pyromeconic acid, yield 25 g. (89%), m.p. 116-117° [lit. (1a) m.p 117°]. The decarboxylation procedure gave yields in the range 40-89%.

Ethyl β-(4*H*-Pyran-4-on-3yloxy)propionate.

A 10-g. sample of ethyl *N*-carboethoxy-β-aminopropionate was converted, *ex situ*, to ethyl β-diazopropionate as previously described (5). Dry, finely ground pyromeconic acid (0.6 g.) was added to the ether solution of the diazo compound in about 10-mg. lots until the rapid evolution of nitrogen gas ceased. The ether solution was dried (magnesium sulfate), and solvent removed under reduced pressure to give 2.87 g. of light yellow oil. The oil, in benzene, was purified by column chromatography on 100 g. of Florisil. The column was developed with 80-ml. quantities of solvents, added in the following order: 1-5, pure benzene; 6, 10% ethanol in benzene; 7-9, 50% ethanol in benzene, and 10, pure ethanol. The eluate was collected in 80-ml. fractions. Evaporation of solvent from fractions 8 and 9 gave a residual yellow oil, which crystallized from cold ether; yield, 250 mg. (22%), m.p. 47-50°, negative ferric chloride test. Colorless needles of ethyl β-(4*H*-pyran-4-on-3-yloxy)propionate, m.p. 48°, were obtained by two additional crystallizations from ether; ir (chloroform): 1743 (ester C=O) and 1647 cm^{-1} (pyrone C=O); nmr (deuteriochloroform): δ 1.22 (t, 3, $COOCH_2CH_3$), 2.65 (t, 2, $O-CH_2-CH_2-CO$), 4.16 (m, 4, $COOCH_2CH_3$ and OCH_2-CH_2CO), 6.25 (d, 1, $C_{(5)}$ pyrone hydrogen), and 7.69 ("t", 2, $C_{(2)}$ and $C_{(6)}$ pyrone hydrogens).

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.58; H, 5.70. Found: C, 55.85; H, 5.55.

β-(4*H*-Pyran-4-on-3-yloxy)propionic Acid.

One g. of ethyl β-(4*H*-pyran-4-on-3-yloxy)propionate was dissolved in 25 ml. of 2*N* hydrochloric acid and heated at 60° for one hour. Upon standing overnight, colorless granular crystals of the acid formed; yield after crystallization from ethanol 685 mg. (79%), m.p. 178-180°. Two additional crystallizations from ethanol gave analytically pure β-(4*H*-pyran-4-on-3-yloxy)propionic acid, m.p. 178-180°; ir (potassium bromide): 3101 (carboxyl OH), 1745 (carboxyl CO), and 1665 cm^{-1} (pyrone CO).

Anal. Calcd. for $C_8H_8O_5$: C, 52.15; H, 4.40. Found: C, 52.29, 52.19; H, 4.52, 4.63.

Attempted Cyclization of β-(4*H*-Pyran-4-on-3-yloxy)propionic Acid.

1. With Polyphosphoric Acid.

To the title acid (250 mg.) was added 8 g. of polyphosphoric acid, and the resulting mixture heated under anhydrous conditions to 120° with stirring. The viscous liquid became dark, and after 2 hours was poured onto ice. The resulting aqueous solution was neutralized with saturated aqueous sodium carbonate and extracted with four 50-ml. portions of chloroform. The extracts were washed with water, dried (magnesium sulfate), filtered, and evaporated under reduced pressure to give a residual yellow solid which was recrystallized from benzene to give pyromeconic acid, m.p. 117-119° [lit. (1a) m.p. 117°], positive ferric chloride test.

This experiment was repeated at temperatures of 60, 80, 100, 120, 140, 160 and 180°, for reaction periods of two to twenty hours, with essentially the same results.

2. With Sulfuric Acid.

A 500-mg. quantity of the title acid was heated with 10 ml. of concentrated sulfuric acid to 100° under anhydrous conditions. The black reaction mixture was poured onto ice and extracted with chloroform. A very low yield of residual solid gave a positive ferric chloride test.

3. With Boron Trifluoride-Acetic Acid Complex.

The title acid (500 mg.) in 5 ml. of acetic anhydride was refluxed two hours with 0.5 ml. of boron trifluoride-acetic acid complex (40% boron trifluoride). Reaction mixture work-up gave unchanged acid.

4. With Phosphoryl Chloride in Benzene.

The title acid (500 mg.) was suspended in 25 ml. of benzene and 5 ml. of phosphoryl chloride. One g. of freshly fused zinc chloride was added and the resulting mixture heated under reflux for 2 hours. Reaction mixture work-up gave unchanged acid.

5. With TFAA.

The title acid (500 mg.), in 5 ml. of freshly distilled trifluoroacetic anhydride, was heated under reflux for fourteen hours. Evaporation of solvent gave a residual oil, which crystallized upon addition of methanol. The solid was collected by filtration (filtrate retained), and identified as unreacted title acid by m.p. and mixed m.p., 178-180°. Evaporation of solvent from the filtrate gave a solid, m.p. 84-86°, which on the basis of spectral data is methyl β-(4*H*-pyran-4-on-3-yloxy)propionate; ir (chloroform): 1748 (ester C=O), 1665 (pyrone C=O); nmr (deuteriochloroform): δ 2.82 ("d", 2, OCH_2CH_2CO), 3.72 (s, 3, $COOCH_3$), 4.22 (t, 2, OCH_2CH_2CO), 6.44 (d, 1, $C_{(5)}$ pyrone hydrogen), 7.73 ("t", 2, $C_{(2)}$ and $C_{(6)}$ pyrone hydrogens). Hydrolysis of the methyl ester in 1 *N* hydrochloric acid through heating for thirty minutes gave the title acid.

6. With Phosphorus Pentoxide in Benzene.

The title acid (500 mg.) was refluxed with 5 g. of phosphorus pentoxide in benzene for two hours. The mixture then was poured onto 25 g. of ice. Unchanged acid precipitated.

7. With Trifluoroacetic Acid (TFA).

The title acid (700 mg.) was heated under reflux for sixteen hours in 10 ml. of TFA, which then was evaporated *in vacuo*. The residual oil was dissolved in water and extracted with three 25-ml. portions of chloroform. The extracts were dried (magnesium sulfate), filtered, and solvent evaporated *in vacuo*. The colorless residue was pyromeconic acid (positive ferric chloride test), m.p. 116-117°.

3-Allyloxy-4*H*-pyran-4-one.

To pyromeconic acid (22.4 g.) in 200 ml. of methanol was added a solution of 10.8 g. of sodium methoxide in 100 ml. of methanol. Allyl bromide (24.1 g.) was then added, and the reaction mixture heated under reflux (with protection from atmo-

spheric moisture) for 2.5 hours. Solvent removal *in vacuo* gave a residue, which dissolved partially in 300 ml. of chloroform. The chloroform solution was decanted, the solid residue dissolved in water and added to the chloroform decantate. The chloroform solution was separated, and the aqueous phase extracted with two 100-ml. portions of chloroform. The combined chloroform extracts were washed with 10% sodium carbonate until a negative ferric chloride test was obtained, dried (magnesium sulfate), filtered, and evaporated *in vacuo*. The residual brown oil crystallized on standing, and was dissolved in warm ether, cooled, and permitted to stand in a freezer overnight. The 3-allyloxy-4*H*-pyran-4-one was obtained as pale tan platelets, mp. 46-48°; yield, 19.3 g. (68%); ir (chloroform): 3012 (C-H str) and 1650 cm^{-1} (pyrone C=O); nmr (deuteriochloroform): δ 4.51 (d, 2, CH_2=CH-C*H*$_2$-O), 5.32 (m, 1, C*H*$_2$=CH-CH_2O), 5.49 (m, 1, C*H*$_2$=CH-CH_2-O), 5.83 (m, 1, CH_2=C*H*-CH_2-O), 6.45 (s, 1, $C_{(5)}$ pyrone H), and 7.72 (d, 2, $C_{(2)}$ and $C_{(6)}$ pyrone hydrogens).

Anal. Calcd. for $C_8H_8O_3$: C, 63.17; H, 5.23. Found: C, 62.81; H, 5.35.

2-Allyl-3-hydroxy-4*H*-pyran-4-one.

3-Allyloxy-4*H*-pyran-4-one was placed in a flask which was flushed several times with dry nitrogen, loosely stoppered, and heated at 170° for thirty minutes. On cooling, there formed a light yellow solid which was recrystallized from ether to give 1.57 g. (83.5%) of 2-allyl-3-hydroxy-4*H*-pyran-4-one, m.p. 83-85° (lit. m.p. 88-89°); ir (chloroform): 3390 (O-H str), 3004 (C-H str), and 1635 cm^{-1} (pyrone C=O); nmr (deuteriochloroform): δ 3.50 (d, 2, CH_2=CH-C*H*$_2$-C), 5.09 (m, 1, C*H*$_2$=CH-CH_2), 5.29 (m, 1, C*H*$_2$=CH-CH_2), 5.73 (m, 1, CH_2=C*H*-CH_2), 6.48 (d, 1, $C_{(5)}$ pyrone H), 7.37 (s, 1, O*H*), and 7.75 (d, 1, $C_{(6)}$ pyrone H).

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(14) Infrared spectra were obtained with a Perkin-Elmer model 237 grating infrared spectrophotometer, for chloroform solutions in a 0.1 mm. cell unless otherwise noted. Nmr spectra were determined on a Varian A60 spectrometer, with TMS as internal standard. Peak multiplicities are indicated by s for singlet, d for doublet, t for triplet, and m for multiplet. Unexpected multiplicities are noted by placing the peak designation in quotation marks.