[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE UNIVERSITY]

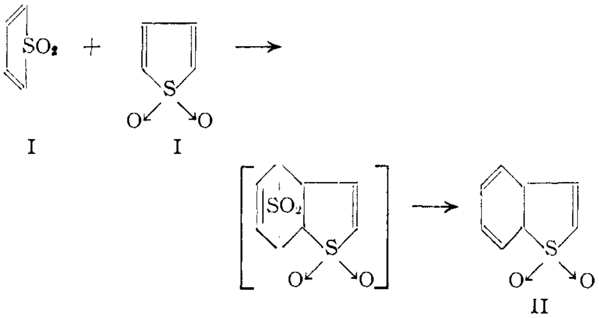
Cyclic Dienes. V. Diels–Alder Reactions of Thiophene 1-Dioxide[1,2]

BY WILLIAM J. BAILEY[3] AND EARL W. CUMMINS

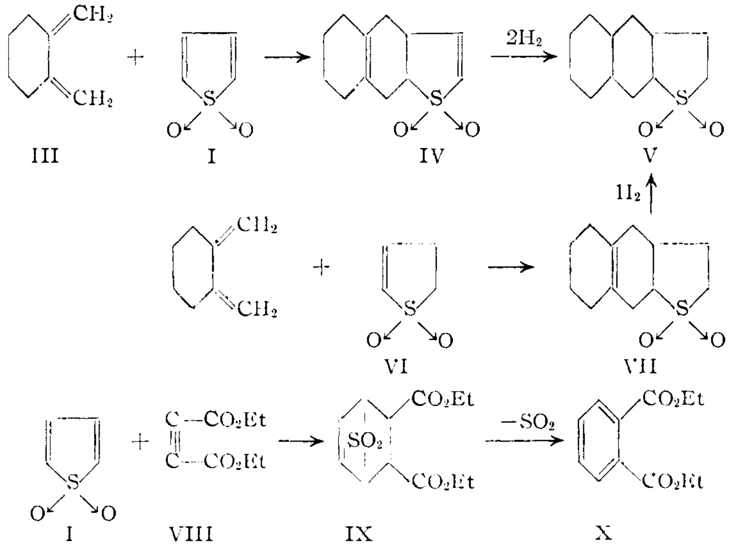
RECEIVED AUGUST 6, 1953

Thiophene 1-dioxide (I) reacts in Diels–Alder reactions as either a diene or a dienophile. With 1,2-dimethylenecyclohexane, it reacted as a reactive dienophile. As an electron-deficient diene, it was not very reactive. Thiophene 1-dioxide (I) did not react with maleic anhydride but added to acetylenedicarboxylic ester and to indene in low yields.

Thiophene 1-dioxide (I) dimerizes with the loss of sulfur dioxide to give 3a,7a-dihydrobenzothiophene 1-dioxide (II).[2] In this reaction one molecule of the dioxide I acts as an electron-deficient diene while the other molecule functions as an electron-deficient dienophile in a typical Diels–Alder reaction. In order to further characterize thiophene 1-dioxide (I) a series of other Diels–Alder reactions were investigated in which it served as either the dienophile or the diene.



Since the sulfone I is strongly electron deficient, it would be expected to react readily as a dienophile with an electron-rich diene in the common-type Diels–Alder reaction. Thus when thiophene 1-dioxide (I) was allowed to stand at room temperature with 1,2-dimethylenecyclohexane (III),[4] $\Delta^{2,4a(8a)}$-octahydronaphtho[2,3-b]thiophene 1-dioxide (IV) was formed. The structure of IV was proved by analysis, ultraviolet absorption and hydrogenation to the dodecahydronaphtho[2,3-b]thiophene 1-dioxide (V). The ultraviolet absorption of IV showed no maximum but increased from an ϵ of 40 at 270 mμ to an ϵ of 565 at 220 mμ. V was synthesized independently from 2,3-dihydrothiophene 1-dioxide (VI). In contrast to the high reactivity of the dienophile I, VI would not add the diene (III) at room temperature but had to be refluxed in a toluene solution for 2 days to produce the $\Delta^{4a(8a)}$-decahydronaphtho[2,3-b]thiophene 1-dioxide (VII). Hydrogenation of VII produced V, which showed no depression in a mixed melting point with a sample of V prepared from thiophene 1-dioxide (I).



As an electron-deficient diene, thiophene 1-dioxide (I) was not as reactive. No adduct could be isolated from the electron-deficient maleic anhydride plus the sulfone I. Apparently the sulfone I dimerized faster than it added to maleic anhydride, indicating that it is more reactive than maleic anhydride as a dienophile. However, with diethyl acetylenedicarboxylate (VIII) aromatization of the final product produced enough driving force to allow the reaction to proceed. Thus VIII and I reacted to form the unstable intermediate (IX) which lost the bridged sulfur dioxide to form diethyl phthalate (X). The liquid X was further identified by hydrolysis, followed by sublimation to yield the known phthalic anhydride (XI), which did not depress the melting point of an authentic sample. In several experiments under mild conditions an unstable solid (IXa), m.p. 105–106°, was isolated. Analysis, molecular weight and saponification equivalent indicated a molecular formula of $C_{12}H_{14}O_6S$. IXa reacted with bromine and potassium permanganate and on gentle heating lost sulfur dioxide to produce diethyl phthalate (X), which was identified by conversion to phthalic anhydride (XI). The ultraviolet absorption of IXa showed no maximum but increased to an ϵ of 3210 at 230 mμ. This unstable solid appears to be an intermediate in the conversion of I to X and can therefore be tentatively assigned the structure of IX.

The usual Diels–Alder reaction is between an electron-rich diene and an electron-poor dienophile. Deno[5] made a study of so-called inverted Diels–Alder reactions in which an electron-poor diene reacts with an electron-rich dienophile. He was able to add muconic acid (XII) to indene (XIII) to form the

---

(1) This work was supported in part by the Office of Naval Research.

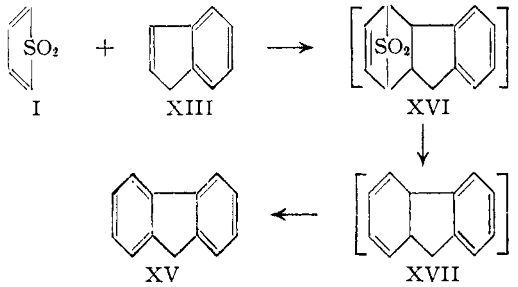
(2) Previous paper in the series, THIS JOURNAL, 76, 1936 (1954).

(3) Department of Chemistry, University of Maryland, College Park, Maryland.

(4) W. J. Bailey and H. R. Golden, THIS JOURNAL, 75, 4780 (1953).

(5) N. C. Deno, *ibid.*, 72, 4057 (1950).

tetrahydrofluorene derivative (XIV) in a 13% yield. It was reasoned, therefore, that the electron-poor I should react as a diene with an electron-rich dienophile such as indene (XIII). Thus I and XIII reacted to form the unstable adduct XVI, which lost sulfur dioxide to form 4a,9a-dihydrofluorene (XVII). XVII was not isolated but its disproportionation product, fluorene (XV), was isolated in low yield. Mixed melting point with an authentic sample of fluorene showed no depression. Therefore, thiophene 1-dioxide (I) appears to be comparable to XII in reactivity as a diene.



These Diels–Alder reactions, together with the ease of dimerization[2] and the ready addition of dimethylamine,[6] indicated there is little or no resonance stabilization in this electron-deficient ring system. In fact, the reverse appears to be true—the thiophene 1-dioxide ring is more reactive in many reactions than an open chain analog or an α,β-unsaturated sulfone.

Experimental[7]

$\Delta^{2,4a(8a)}$-Octahydronaphtho(2,3-b)thiophene 1-Dioxide (IV).—To the cold chloroform extracts, dried over magnesium sulfate, resulting from the decomposition of 10 g. (0.33 mole) of 3-dimethylamino-2,3-dihydrothiophene 1-dioxide methiodide and presumed to contain 2.52 g. (0.0434 mole) of thiophene 1-dioxide (I) (based on the reaction with dimethylamine),[6] was added 2.35 g. of 1,2-dimethylenecyclohexane (III). After standing for 42 hours at room temperature, the reaction mixture was separated from a small amount of insoluble oil, evaporated at atmospheric pressure to a volume of about 25 ml. during a 1.5-hour period, and again separated from an additional small amount of insoluble oil. The resulting chloroform solution was then evaporated to dryness at room temperature, under a slight vacuum, to give 3.64 g. of medium red oil.

The unreacted 1,2-dimethylenecyclohexane (1.21 g.) was removed from the impure product by trituration with petroleum ether to give a light yellow oil which crystallized on standing. Recrystallization from an aqueous ethanol solution gave 2.43 g. [50% yield based on the diene III originally used] of a pure white needles of $\Delta^{2,4a(8a)}$-octahydronaphtho(2,3-b)thiophene 1-dioxide (IV), m.p. 89–89.5°.

Anal. Calcd. for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.14. Found: C, 64.50; H, 7.30.

$\Delta^{4a(8a)}$-Decahydronaphtho(2,3-b)thiophene 1-Dioxide (VII).—A suspension (which became homogeneous on heating) of 1.00 g. (0.00847 mole) of 2,3-dihydrothiophene 1-dioxide (VI),[6] in a solution of 4.60 g. (0.0424 mole) of 1,2-dimethylenecyclohexane (III) plus a trace of N-phenyl-β-naphthylamine in 25 ml. of toluene, was placed in a 50-ml. flask and refluxed for 44 hours. The reaction mixture was then evaporated to dryness under partial vacuum to give a mixture of a light yellow oil and solid, which contained a large amount of unreacted VI plus polymeric material. This oil and solid mixture was triturated with ether and the ether triturates were evaporated to dryness to give a solid-free yellow oil. This oil was taken up in the minimum amount of petroleum ether and cooled to −10° to give a light yellow crystalline solid, m.p. 63–66°. Recrystallization from an ethanol–water mixture produced 0.20 g. (10%) of pure $\Delta^{4a(8a)}$-decahydronaphtho(2,3-b)thiophene 1-dioxide (VII), m.p. 71–72°.

Anal. Calcd. for $C_{12}H_{18}O_2S$: C, 63.71; H, 7.56. Found: C, 64.02; H, 7.85.

Dodecahydronaphtho(2,3-b)thiophene 1-Dioxide (V). A. By the Hydrogenation of $\Delta^{2,4a(8a)}$-Octahydronaphtho-(2,3-b)thiophene 1-Dioxide (IV).—A solution of 0.0874 g. (0.00039 mole) of $\Delta^{2,4a(8a)}$-octahydronaphtho(2,3-b)thiophene 1-dioxide (IV) in 15 ml. of glacial acetic acid, plus 0.1 g. of prereduced PtO_2, was subjected to low pressure hydrogenation. The up-take was 16.45 ml. of hydrogen (0° and 760 mm.) (92% of theory) in 18 minutes. The catalyst was filtered off and the filtrate evaporated to dryness to give a light yellow oil which crystallized on standing. Recrystallization from ethanol–water gave 0.048 g. (55%) of pure white flakes of dodecahydronaphtho(2,3-b)thiophene 1-dioxide (V), m.p. 90–91°.

Anal. Calcd. for $C_{12}H_{20}O_2S$: C, 63.16; H, 8.75. Found: C, 62.96; H, 8.92.

B. By the Hydrogenation of $\Delta^{4a(8a)}$-Decahydronaphtho(2,3-b)thiophene 1-Dioxide (VII).—A solution of 0.0847 g. (0.000374 mole) of $\Delta^{4a(8a)}$-decahydronaphtho(2,3-b)thiophene 1-dioxide (VII) in 15 ml. of acetic acid plus 0.1 g. of prereduced PtO_2 was reduced with low pressure hydrogenation. The up-take of hydrogen was 9.7 ml. (115% of theory) in 40 minutes. Removal of the catalyst, evaporation to dryness and crystallization from ethanol-water gave 0.052 g. (60%) of pure white flakes of dodecahydronaphtho(2,3-b)-thiophene 1-dioxide V), m.p. 91–92°. A mixed melting point with the sample of V prepared from IV as described above showed no depression.

Diethyl Phthalate (X).—The cold, dry chloroform extracts resulting from the decomposition of 8.63 g. (0.0285 mole) of 3-dimethylamino-2,3-dihydrothiophene 1-dioxide monomethiodide and assumed to contain 2.62 g. (0.0188 mole) of thiophene 1-dioxide (I) (based on the reaction with dimethylamine) were allowed to stand for 2 days with 3.80 g. (0.0224 mole) of diethyl acetylenedicarboxylate (VIII). The reaction mixture was refluxed for an additional 4 hours and the chloroform removed under reduced pressure to obtain an oil. Extraction of this residue with petroleum ether, followed by distillation, yielded 0.9 g. (18% based on VIII) of diethyl phthalate (X), b.p. 108–112° (1 mm.), $n^{25}\text{D}$ 1.5005, after removal of the unreacted VIII. A small sample of X was saponified with alcoholic sodium hydroxide, acidified with concentrated hydrochloric acid, and evaporated to dryness. Sublimation under a partial vacuum of 6 mm. gave long white needles of phthalic anhydride (XI), m.p. 128–129° (sealed tube). A mixed melting point (sealed tube) with an authentic sample of phthalic anhydride (XI) showed no depression.

Thiophene 1-Dioxide–Diethyl Acetylenedicarboxylate Adduct (IXa).—To the cold, dry chloroform extracts resulting from the decomposition of 8.63 g. (0.0285 mole) of 3-dimethylamine-2,3-dihydrothiophene 1-dioxide monomethiodide and assumed to contain 2.62 g. (0.0188 mole) of thiophene 1-dioxide (I) (based on the reaction with dimethylamine), was added 3.80 g. (0.0224 mole) of diethyl acetylenedicarboxylate (VIII). The resulting solution was evaporated to dryness over a period of 3 to 4 hours, under a vacuum of 20 to 30 mm., while the pot temperature was maintained below 0°. During the evaporation the solution became green, in contrast to the yellow color observed when only thiophene 1-dioxide was present. When all the solvent had been removed, the resulting light green oil was allowed to stand for 15 minutes at room temperature with no apparent change; however, when air was admitted, solid immediately precipitated.

Six recrystallizations from chloroform–ether gave 0.94 g. (16% based on the methiodide) of pure white needles of a thiophene 1-dioxide–diethyl acetylenedicarboxylate adduct (IXa), m.p. 105–106° dec.

(Results of the reaction were somewhat erratic and could not be duplicated every time.)

Anal. Calcd. for $C_{12}H_{14}O_6S$: C, 50.35; H, 4.88; mol. wt., 286; sapon. equiv., 143. Found: C, 50.48; H, 5.05; mol. wt. (cryoscopic in benzene), 297; sapon. equiv., 146.8.

IXa reacted slowly with bromine in chloroform, rapidly

---

[6] W. J. Bailey and E. W. Cummins, THIS JOURNAL, **76**, 1932 (1954).

[7] The authors are indebted to Vivian Kapuscinski, James French, Robert Keen and Arthur Tomesewski for the analyses. All melting points are corrected.

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

[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

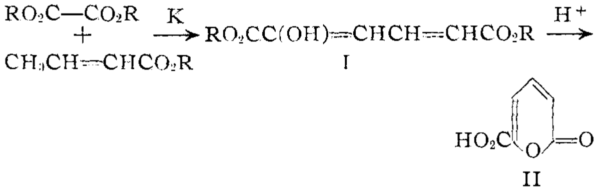
BY RICHARD H. WILEY AND ALBERT J. HART

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



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

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

---

[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).