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2,3-Di-(2-thienyl)-2,3-butanediol (I)

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Certain pinacolones and indenones, derived from the mono-dehydration (pinacol-pinacolone rearrangement) and double-dehydration of methyl pyridyl glycols, have been reported to function as specific inhibitors of 11- β -hydroxylase in the biosynthesis of corticoid hormones (3,4).

Since the methyl pyridyl glycols required in the previous work were readily available from the bimolecular photoreduction of the parent methyl pyridyl ketones, an attempt was made to synthesize the glycol analogs of the five-membered heterocyclic systems in this fashion. We have previously reported a general indene cyclodehydration of similar diols in the methyl phenyl series (5).

2-Propanol solutions of the 2-acetyl and 3-acetyl thiophenes, 2-acetylpyrrole and 2-acetylfuran were irradiated at a high pressure mercury arc for 48-hour periods. Unreacted starting materials were recovered in 90% or greater yield. Similar results have been reported in the irradiation of 2-benzoylfuran (6).

Following the suggestion of Porter (7) that carbonyls substituted on strongly electron releasing rings sometimes show a lack of photoreductive activity in alcoholic medium due to the intercession of an intramolecular charge-transfer state, we carried out irradiations in cyclohexane, a solvent reported to assure that the required $n-\pi^*$ triplet is the lower energy state (8). These irradiations were likewise unsuccessful in producing the desired diols.

An interesting reflection of the reported influence of electron density on the carbon adjacent to a carbonyl as responsible for elevating the energy required for an $n-\pi^*$ excitation (9) is observed in these heterocyclic ketones. Molecular orbital and valence bond calculations of π densities in heterocycles show that all of the five-membered systems (pyrrole, furan, and thiophene) have values greater than unity for the ring carbons (10). Similar calculations for the pyridine ring show that although all ring carbons show π densities less than unity, the β carbon is the most electron rich.

Bencze, Burckhardt and Yost (4) have reported that the ease of photoreduction of the methyl pyridyl ketones was inversely related to these known ring densities. This observation, coupled with our results that the π -excess heterocyclic ketones are non-photoreductive, points to the possibility that in furan, thiophene, and pyrrole carbonyl compounds the $\pi-\pi^*$ triplet may be of lower energy than the $n-\pi^*$ triplet required for photoreductions (11).

The aluminum amalgam bimolecular reduction technique (12) was employed on 2-acetylthiophene. None of the desired 2,3-di-(2-thienyl)-2,3-butanediol could be isolated from the reaction mixture. Its presence as an intermediate was indicated by the fact that 56% of the isolated product was identified as its pinacolone, 3,3-di-(2-thienyl)-2-butanone. The authentic diol, prepared by the Grignard method, was observed to yield the pinacolone by refluxing with a benzene suspension of the amalgamating agent, mercuric chloride.

The desired glycol was synthesized in 6.5% yield by the addition of 2-thienylmagnesium iodide to 2,3-butanedione. Rearrangement in dilute sulfuric acid led to its quantitative conversion to 3,3-di-(2-thienyl)-2-butanone. Gas chromatographic analysis revealed the absence of the other possible pinacolone isomer. Product assignment was facilitated by the single non-conjugated ketone carbonyl at 1735 cm^{-1} in the infrared and by the non-equivalent methyl resonance singlets at 1.52 and 2.10 ppm (CCl_4 solvent, TMS reference) in the nmr.

Efforts to employ the polyphosphoric acid dehydration method (5) led to tarry residues from which no indene product could be isolated.

In keeping with previous reports that diols which could not be prepared by photoreduction methods could sometimes be photooxidized by irradiation in acetone, the photooxidizability of the thiophene glycol was explored (13). Irradiation in acetone for 48 hours gave approximately 40% yield of 2-acetylthiophene.

EXPERIMENTAL

Combustion analyses were performed by Dr. Alfred Bernhardt at the Max-Planck-Institut für Kohlenforschung, Mülheim, Ruhr. Infrared spectra were scanned as Nujol mulls on a Perkin Elmer 237 spectrophotometer and peak positions are reported as calibrated against the polystyrene standard. Gas chromatographic separations were carried out on an Aerograph A-350 on ten foot GE-SF 96 on firebrick.

2,3-Di-(2-thienyl)-2,3-butanediol.

To the Grignard reagent prepared from 0.35 g. atom of magnesium turnings and 0.35 mole of 2-iodothiophene in 200 ml. of dry ether was added a solution of 0.10 mole of 2,3-butanedione and 10 ml. of dry ether. The mixture was stirred at room temperature for 12 hours and hydrolyzed by pouring over chopped ice containing 6 N hydrochloric acid. The ether extraction layer was washed with 10% sodium hydrogen sulfite solution and then with saturated sodium chloride solution and dried over magnesium sulfate.

Evaporation produced a green-blue oil which could not be induced to crystallize. By chromatography on a 2.5 x 25 cm. column of activated alumina using successive hexane-benzene-methanol eluants, three distinct fractions could be isolated. The first fraction was a yellow oil whose infrared spectrum showed it to be a mixture of 2,3-butanedione and 2-iodothiophene. The second fraction was a viscous green-blue oil that deposited white crystals on standing. Three recrystallizations from benzene gave 1.63 g. (6.5%) of the diol, m.p. 117°.

Anal. Calcd. for $C_{12}H_{14}O_2S_2$: C, 56.65; H, 5.55. Found: C, 56.81; H, 5.55.

The infrared spectrum revealed a strong -OH absorption band at 3600 cm^{-1} and thiophene ring bands at 710 cm^{-1} .

The third fraction from the chromatographic separation was a viscous sulfurous smelling oil. Vacuum distillation at 26 mm. of Hg gave 8.2 g. of 2-acetylthiophene, b.p. 110-112° and 1.8 g. of 3,3-di-(2-thienyl)-2-butanone, b.p. 199-201°. These substances were identified by peak enhancement gas chromatography and infrared spectral comparison with authentic samples (14).

3,3-Di-(2-thienyl)-2-butanone.

A solution of 150 mg. of the diol, 5.0 ml. of glacial acetic acid, and 1.0 ml. of concentrated sulfuric acid was warmed for one hour on a steam bath. After hydrolysis with cold water, neutralization with aqueous sodium carbonate solution and extraction with ether, the ethereal layer was washed with saturated sodium chloride solution until neutral. The dried and concentrated organic phase was examined by infrared spectroscopy and revealed no unreacted diol. Gas chromatography displayed a single component. An oxime prepared by the pyridine method melted at 171-172°.

Anal. Calcd. for $C_{12}H_{14}NOS_2$: C, 57.34; H, 5.21; N, 5.57. Found: C, 57.65; H, 5.19; N, 5.61.

Irradiation of Heterocyclic Ketones.

One molar solutions of 2-acetylthiophene (Columbia Organic Chemicals), 2-acetylpyrrole (15), 2-acetylfuran (16), and 3-acetylthiophene (17) were dissolved in reagent grade 2-propanol, degassed, and sealed in quartz tubes. The tubes were positioned at 6.5 cm. from an Hanovia SH-616A mercury vapor lamp provided with a vycor heat shield and a blower for heat exhaust. After 48 hours the tubes were cooled and opened; vpc analysis showed that no reaction had occurred.

Irradiation of 2,3-Di-(2-thienyl)-2,3-butanediol.

A solution of 100 mg. of the diol in 2.5 ml. of freshly distilled reagent grade acetone was prepared as described above and exposed for 48 hours. Gas chromatographic analysis demonstrated the presence of approximately 40% of 2-acetylthiophene. The remaining material was identified by infrared spectroscopy as unreacted diol.

Aluminum Reduction of 2-Acetylthiophene.

A paste formed from 4.5 g. of 30 mesh aluminum, 1.8 g. of mercuric chloride and 5.0 ml. of anhydrous benzene was heated and stirred for 5 minutes in a 3 neck round bottom flask. Freshly distilled 2-acetylthiophene, 31.5 g. in 25 ml. of benzene, was added dropwise and heating was continued for 3 more hours. The mixture was cooled, diluted with 18 ml. of benzene and hydrolyzed by dropwise addition of water. The precipitated solids were filtered, washed

well with ether, and the organic layer of the filtrate was dried over sodium sulfate. Removal of solvents gave an oil which was vacuum distilled to recover unreacted 2-acetylthiophene (9.0 g.), b.p. 60-61° at 1.5 mm. of Hg and 3,3-di-(2-thienyl)-2-butanone (17.8 g.) b.p. 138-140° at 1.5 mm. of Hg. Even in the absence of distillation, no diol could be detected spectrally in the reaction product.

When the authentic 2,3-di-(2-thienyl)-2,3-butanediol (50 mg.) was refluxed with 10 ml. of benzene and 50 mg. of mercuric chloride for 24 hours, it was converted quantitatively into 3,3-di-(2-thienyl)-2-butanone. Evaporation of the benzene filtrate, after removal of the suspended mercuric chloride, gave an oil which was spectrally identical with the pinacolone.

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Received April 29, 1966

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