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Intramolecular Diels-Alder Cyclization into the Thiophene Ring (1)

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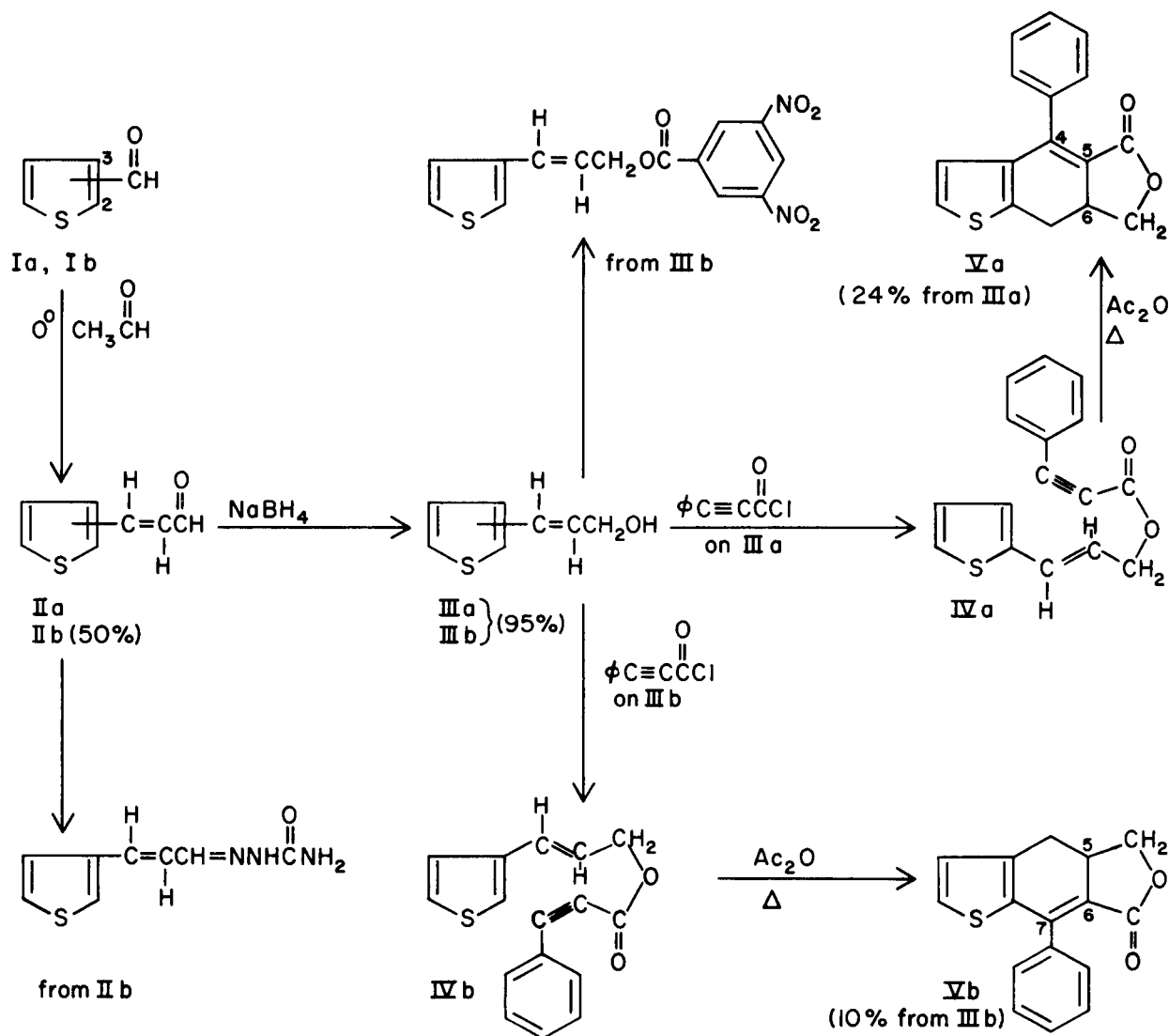
Trans-3-(2- and 3-thienyl)allyl alcohols have been prepared from the corresponding acroleins. The esters of these alcohols with phenylpropionic acid underwent intramolecular Diels-Alder reactions to give the substituted dihydrothianaphthene lactones Va and Vb, respectively.

The similarity between the benzene and the thiophene rings in reactivity as dienes in the thermal, intermolecular Diels-Alder reaction has been noted in the literature. Thus, neither benzene nor thiophene forms an adduct with maleic anhydride (3,4), while both styrene and 2-vinylthiophene undergo reaction with maleic anhydride and other dienophiles (5-7). Although the synthesis of 3-vinylthiophene has been accomplished (8), no study of the action of this compound as a diene appears to have been made. In two earlier papers we reported the syntheses of substituted *trans*-cinnamyl phenylpropiolates (9) and their intramolecular Diels-Alder reactions (by thermal processes) (10) to form lignans of the 1-aryl-3-hydroxymethyl-3,4-dihydro-2-naphthoic acid lactone type. We have since effected the same intramolecular reaction on the parent enynic ester itself, namely *trans*-cinnamyl phenylpropiolate, A (11). In the intramolecular Diels-Alder reaction of A, just as in the intermolecular reaction of styrene, the dienophilic moiety adds in a 1,4-manner to the phenylvinyl group, whereby substitution into the benzene ring occurs. The present paper concerns the synthesis of the thiophene analogs (isosters) of A, *trans*-3-(2- and 3-thienyl)allyl phenylpropiolates (IVa and IVb) and their subsequent intramolecular Diels-Alder reactions to form the corresponding lactones Va and Vb, respectively. Formation of Va involves substitution into the 3-position of thiophene, while formation of Vb involves substitution into the 2-position of this heterocycle. The synthetic procedures used are outlined in Scheme I.

Aldol condensation of thiophene-2- and -3-aldehydes with acetaldehyde in the presence of ethanolic sodium hydroxide at 0° gave the corresponding acroleins, IIa and IIb. Acrolein IIa has been prepared previously by Keskin, Miller, and Nord (12) by this procedure. Both IIa and IIb are liquids which can be purified by rapid distillation *in vacuo* but which decompose appreciably if the distillation is conducted slowly. Reduction of the acroleins to the thienylallyl alcohols IIIa and IIIb was effected in very high

yield by means of ethanolic sodium borohydride. Reaction of these allylic alcohols with phenylpropionyl chloride in benzene and pyridine gave the crude enynic esters IVa and IVb, which were cyclized by means of refluxing acetic anhydride to the substituted dihydrothianaphthene lactones Va and Vb, respectively.

Before one could feel entirely sure that these cyclizations in the thienyl series were analogous to the reaction of A, it was pertinent to ascertain that the esters IV did, indeed, contain a *trans*-thienylvinyl group. Since the conversion of I to IV involved basic reaction conditions at each step it appeared likely that the geometric configuration would remain the same as that established in the original acrolein II. It was anticipated that this would be *trans*, as reported for the configuration of crotonaldehyde which results from base-catalyzed dehydration of aldol itself (13) and as rationalized from the experimental observation that the mechanisms of various base-catalyzed aldol condensations appear to be similar, *i.e.* to involve first the formation of a β -hydroxyaldehyde (or β -hydroxyketone) by means of a series of reversible steps and then, in certain cases, the irreversible dehydration of this intermediate (14). Spectral examination of four (IIIb, IIIc, IVa, and IVb) of the six compounds involved in our studies did indicate that the *trans* configuration was present. Thus, the infrared spectrum of each of these compounds showed a medium to strong absorption band at $960 \pm 5 \text{ cm}^{-1}$, believed to be due to C-H out-of-plane bending for the *trans* grouping CH=CH (9,15). This band (as well as the band at *ca.* 2200 cm^{-1} due to the presence of a carbon-carbon triple bond) disappeared on refluxing IVa and IVb with acetic anhydride to effect cyclization to Va and Vb, respectively. Consistent with this process of cyclization was also the bathochromic shift of the carbonyl absorption band by $40 \pm 5 \text{ cm}^{-1}$ (16). The n.m.r. spectrum of 3-(3-thienyl)allyl alcohol (IIIb), moreover, served to markedly strengthen the *trans* assignment. Thus, this spectrum showed



a: For 2-thienyl series b: For 3-thienyl series
 SCHEME I

a doublet of triplets (corresponding to a total of one proton) centered at $\delta = 5.87$ and 6.14 p.p.m. (*i.e.* $J = 18$ c.p.s. for the separation of centers--primary splitting) and with an internal (secondary) splitting of 5 c.p.s. in each triplet. This splitting pattern is the one expected for the hydrogen atom on the central (β -) carbon atom of the side chain $\text{CH}=\text{CHCH}_2\text{OH}$. The primary splitting is assigned to a *trans* hydrogen atom (17) (α - to the ring) and the secondary splitting, to the methylene group. Correspondingly, the methylene group absorption occurred

as a doublet at 4.1 p.p.m. with $J = 5$ c.p.s. Unfortunately, the complete doublet expected for the α -H could not be cleanly observed. There was a sharp band (corresponding to less than one proton, at 6.47 p.p.m.) which is believed to be the upfield half of the expected doublet. The downfield portion of this doublet appears to be superimposed on the first band of the aromatic proton absorption complex in the region of 6.6 - 7.2 p.p.m., where total integration indicates more than three protons (expected for the aromatic group) but fewer than four protons.

EXPERIMENTAL (18)

trans-3-(3-Thienyl)acrolein (IIb).

To a cold (< 0°), vigorously stirred solution of 2.1 g. of thiophene-3-carboxaldehyde (19) and 0.5 g. of sodium hydroxide in 8 ml. of 35% ethanol was added, over a period of two hours, 5 ml. of a 40% aqueous solution of acetaldehyde. The mixture was stirred at 0° for 15 minutes longer, neutralized with ice-cold 20% acetic acid, and extracted with benzene. The benzene extract was washed first with dilute aqueous sodium bicarbonate solution and then with water, dried with anhydrous sodium sulfate and evaporated under reduced pressure. The residual liquid was distilled *in vacuo*, b.p. *ca.* 125-128° (5 mm.) yield 1.3 g. (50%); infrared absorption bands (neat) at 1680 (α,β -unsaturated aldehyde) and 965 (*trans* CH=CH) cm^{-1} .

The semicarbazone derivative (20, method B) was recrystallized from methanol to give cream-colored prisms, m.p. 215-216° (dec.).

Anal. Calcd. for $\text{C}_8\text{H}_9\text{N}_3\text{OS}$: C, 49.21; H, 4.65; N, 21.52; S, 16.42. Found: C, 49.12; H, 4.57; N, 21.50; S, 16.33.

trans-3-(Thienyl)Allyl Alcohol (IIIb).

To a stirred solution of 1 g. of 3-(3-thienyl)acrolein in 3 ml. of ethanol was added, at room temperature, a solution of 0.1 g. of sodium borohydride in 5 ml. of ethanol. The mixture was stirred for one hour and evaporated *in vacuo*. The residue was treated with 10 ml. of water for 30 minutes in order to hydrolyze borate esters and the mixture was extracted with ether. The residue from evaporation of the dried ether layer was distilled, b.p. *ca.* 140-145° (12 mm.), to give 1 g. (essentially quantitative yield) of liquid which solidified on cooling. Recrystallization from petroleum ether (60-90°) gave white crystals, m.p. 52-53°; infrared absorption bands (CHCl_3) at 3430 (OH) and 960 cm^{-1} (*trans* CH=CH); n.m.r. absorptions (CDCl_3) at $\delta = 3.7$ (broad peak, OH), 4.1 (broad doublet, methylene, $J = 5$ c.p.s.), 5.87 and 6.14 (a doublet of triplets with primary splitting: $J = 18$ c.p.s., secondary splitting: $J = 5$ c.p.s., proton on carbon adjacent to CH_2OH group), 6.47 (a sharp band corresponding to less than one proton), and 6.6-7.2 p.p.m. (multiplet, between 3 and 4 protons).

The 3,5-dinitrobenzoate derivative was prepared by heating a mixture of 0.2 g. of the alcohol, 2 ml. of pyridine, and 0.5 g. of 3,5-dinitrobenzoyl chloride on a steam bath for 30 minutes. Water was added and the mixture was reheated briefly. A chloroform extract of the mixture was washed successively with dilute hydrochloric acid, dilute aqueous sodium bicarbonate solution, and water, dried, and evaporated. A solution of the red residue in ethyl acetate was successively treated with methanol, concentrated, and filtered until a dark red precipitate (discarded) was no longer formed. Concentration of the resultant, yellow mother liquor produced greenish crystals, m.p. 110-114°, converted to cream-colored prisms (m.p. 116-117°) on recrystallization from methanol.

Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_6\text{S}$: C, 50.29; H, 3.02; N, 8.38; S, 9.59. Found: C, 49.96; H, 3.06; N, 8.60; S, 9.33.

7-Phenyl-5-hydroxymethyl-4,5-dihydrothianaphthene-6-carboxylic Acid Lactone (Vb).

A mixture of 1.2 g. of phenylpropionic acid (Aldrich Chemical Co., Milwaukee, Wis.), 1 ml. of reagent grade thionyl chloride, and 3 ml. of benzene was refluxed for 1.5 hours. Excess thionyl chloride was removed by repeated azeotropic distillation of the mixture with benzene. To an ice-cold, stirred solution of the residue (acid chloride) in 10 ml. of benzene was added 2 ml. of pyridine and then (slowly) a solution of 1 g. of alcohol IIIb in 5 ml. of benzene. The mixture was refluxed for 5 hours and allowed to stand overnight. The benzene layer was separated, washed successively with dilute hydrochloric acid, dilute aqueous sodium bicarbonate solution, and water, dried, and evaporated. The brown liquid residue (1 g.), presumably crude ester IVb, showed infrared absorption bands (CHCl_3) at 2220 ($\text{C}\equiv\text{C}$), 1710 (ester C=O), and 965 cm^{-1} (*trans* CH=CH).

A solution of 0.6 g. of this crude ester in 3 ml. of acetic anhydride was refluxed for 6 hours and evaporated under reduced pressure. The resultant residue was treated with water and extracted with chloroform. The chloroform extract was washed with dilute aqueous sodium bicarbonate solution and then with water, dried, and evaporated. Column chromatography of the residue using neutral alumina and benzene (followed by benzene-5% ethyl acetate) gave an initial oily fraction (discarded) and then fractions (retained) which crystallized on scratching in the presence of petroleum ether. Recrystallization from petroleum ether (40-60°) gave cream-colored needles of Vb, yield 120 mg. (10% from IIIb), m.p. 155-156°; infrared absorption band (α,β -unsaturated γ -lactone C=O) at 1745 cm^{-1} , no absorptions near 2220 or 965 cm^{-1} .

Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{O}_2\text{S}$: C, 71.62; H, 4.51; S, 11.95. Found: C, 71.87; H, 4.47; S, 11.76.

trans-3-(2-Thienyl)allyl Alcohol (IIIa).

To a stirred, cooled (in a cold water bath) solution of 5 g. of 3-(2-thienyl)acrolein (12) in 12 ml. of absolute ethanol was added, over a period of 10 minutes, a solution of 0.4 g. of sodium borohydride in ethanol. Further processing in the manner used for preparation of the isomer IIIb gave 4.8 g. (95%) of liquid IIIa, b.p. 137-140° (12 mm.). An analytical sample was obtained as a colorless liquid after redistillation, b.p. 113-114° (3 mm.).

Anal. Calcd. for $\text{C}_7\text{H}_8\text{OS}$: C, 59.96; H, 5.75; S, 22.87. Found: C, 60.21; H, 6.11; S, 23.45.

4-Phenyl-6-hydroxymethyl-6,7-dihydrothianaphthene-5-carboxylic Acid Lactone (Va).

To an ice-cold, stirred solution of phenylpropionyl chloride (prepared from 5 g. of phenylpropionic acid in the aforementioned manner) in a mixture of 5 ml. of pyridine and 55 ml. of benzene was added dropwise a solution of 4.6 g. of alcohol IIIa in 50 ml. of benzene. Refluxing and subsequent processing were conducted in the manner used for synthesis of the isomer IVb. The brown, oily ester IVa (6 g.) showed infrared absorption bands (neat) at 2200 ($\text{C}\equiv\text{C}$), 1710 (ester C=O), and 955 cm^{-1} (*trans* CH=CH).

Cyclization of this crude ester by refluxing with 20 ml. of acetic anhydride for 6 hours and then further processing in the manner used for preparation of the isomer Vb gave several tan to brown solid chromatographic fractions. Crystallization of these solids from benzene-petroleum ether (40-60°) produced 2.1 g. (24%) of tan Va, m.p. 135-139°. Recrystallization from petroleum ether and then from benzene-petroleum ether gave faintly tan needles, m.p. 141-142°; infrared absorption bands (CHCl_3) at 1755 cm^{-1} (α,β -unsaturated γ -lactone C=O), no absorptions near 2200 and 955 cm^{-1} .

Anal. Calcd. for $\text{C}_{18}\text{H}_{12}\text{O}_2\text{S}$: C, 71.62; H, 4.51; S, 11.95. Found: C, 71.57; H, 4.49; S, 10.68 (21).

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