

undepressed, and the infrared spectra of these two products were superimposable.

Dimethyl 4,4'-Dithiobiscinnamate.¹³—Into a three-necked flask fitted with a gas-inlet tube and reflux condenser were placed 0.5 g. (0.0014 mole) of 4,4'-dithiobiscinnamic acid and 50 ml. of absolute methanol. A gentle stream of dry hydrogen chloride gas was introduced into the mixture for 12 hr. accompanied by gentle refluxing. The insoluble material was removed and the filtrate concentrated. The isolated solid product was washed with warm 5% aqueous sodium bicarbonate and recrystallized from dilute ethanol to give 0.1 g. (20%) of white plates, m.p. 134–135°.

Methyl *p*-Ethylmercaptocinnamate.—Using a reported general procedure,²⁸ *p*-ethylmercaptocinnamic acid (1.04 g. 0.005 mole) was treated with thionyl chloride, and the excess thionyl chloride removed under diminished pressure, leaving a residual yellow oil. About 25 ml. of absolute methanol was then carefully added to the residue and this mixture refluxed for 3 hr. The product crystallized from the reaction mixture to give 0.9 g. (81%) of crude product, m.p. 65–70°. The material was recrystallized several times from dilute ethanol to give white plates, m.p. 72–73°.

***p*-Mercaptobenzoic Acid.**—A convenient modification of the procedure of Allen and MacKay⁸ was used. A mixture of 290 ml. of water, 260 g. (1.1 moles) of crystallized sodium sulfide ($\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$), and 34 g. of powdered elemental sulfur was placed in a 4-l. beaker and warmed to effect solution. A solution of 40 g. of sodium hydroxide pellets in 100 ml. of water was then added and the mixture cooled in an ice bath to 5°. Into a 2-l. beaker, set in an ice bath and provided with a stirrer and a thermometer, were placed 500 ml. of water, 137 g. (1.0 mole, Eastman Practical Grade) of *p*-aminobenzoic acid, and 200 ml. of concentrated hydrochloric

acid. When the temperature of the mixture had fallen to 5°, a solution of 69 g. (1.0 mole) of sodium nitrite in 280 ml. of water was added from a dropping funnel whose tip extended below the surface of the liquid. The addition required about 15 min. and cracked ice was added to keep the temperature below 5°. The stirrer was then transferred to the alkaline sulfide solution and the diazonium salt solution added over a 0.5-hr. period, keeping the temperature below 5°. The mixture was allowed to warm slowly to room temperature accompanied by the evolution of nitrogen gas. The solution was made acid to Congo red paper with 180 ml. of concentrated hydrochloric acid and the precipitated, crude disulfide collected with suction. The product was reprecipitated from warm 10% aqueous sodium carbonate solution, collected, and dried in the air, giving 150 g. (98%) of crude material, m.p. 315–320°.

A mixture of crude 4,4'-dithiobisbenzoic acid (31 g., 0.1 mole) and 20 g. of zinc dust was suspended in 250 ml. of glacial acetic acid in a flask fitted with a motor-driven stirrer and a reflux condenser. The reaction mixture was stirred vigorously under reflux for 6 hr. Several additional small portions of zinc dust were added during this period. The solid materials were collected by suction, washed in 250 ml. of hot water, recollected, and placed into 250 ml. of hot water to which was added a solution of 25 g. of sodium hydroxide pellets in 50 ml. of water. The alkaline solution was heated for about 5 min., filtered to remove the insoluble impurities, and the filtrate acidified immediately. The white product was collected, pressed as dry as possible, and dried in a vacuum desiccator over potassium hydroxide. The yield was 21 g. or 68%, m.p. 216–219°. A sample was sublimed at 205° and 0.1 mm. pressure to give a white powder, m.p. 216–217°. The reported melting point is 219°.²⁹

(28) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green, and Co., London, 3rd ed., 1956, p. 784.

(29) I. Heilbron, "Dictionary of Organic Compounds," Vol. III, Oxford University Press, New York, N. Y., 1953, p. 248.

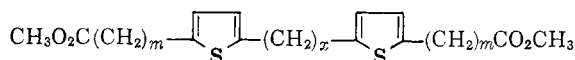
An Investigation of Some Approaches to the Synthesis of α -Cyclodipolymethylenedithiophenes

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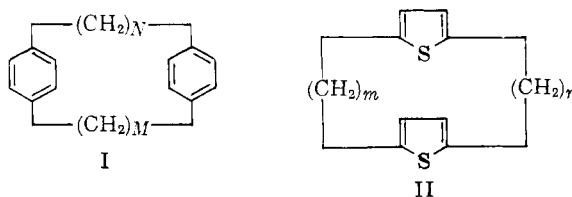
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Esters having the general structure,



($x = 1, m = 3$; $x = 1, m = 5$; $x = 6, m = 2$; and $x = 6, m = 3$), were synthesized from thiophene and subjected to high dilution intramolecular acyloin condensations in an attempt to prepare thiophene analogs (II) of the paracyclophanes. In all cases studied, no evidence for a cyclic structure was obtained. However, a linear acyloin, 3-hydroxy-4-keto-1,6-bis(2'-thienyl)hexane, could be obtained from ethyl β (2-thienyl)propionate.

The investigation reported here was partially suggested by the study of Cram and his collaborators³ on the properties of cyclic molecules involving benzene rings, the paracyclophanes (I). These compounds were shown to possess unusual chemical and physical properties,³ due to modification of the



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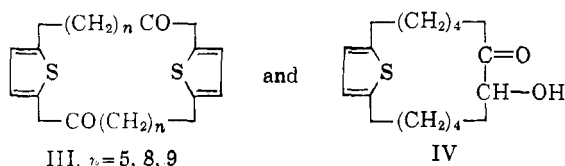
(3) D. J. Cram, W. J. Wechter, and R. W. Kurstead, *J. Am. Chem. Soc.* **80**, 3126 (1958) and references cited.

benzenoid resonance resulting from bowing of the benzene rings toward one another, to transannular effects, and to restricted rotation of the benzene

rings where one of the rings is monosubstituted, and M and N are small.

Thus, it appeared to be of considerable interest to investigate the synthesis and properties of the thiophene analogs of the paracyclophanes, the α -cyclo-dipolymethylenedithiophenes (II). The latter compounds due to their structural features would undergo some chemical reactions not possible in the paracyclophanes. The large sulfur atom should cause pi electron cloud interaction and consequent alteration in their aromatic resonance with shorter polymethylene chains. Further, it should be possible to identify one or both of the possible isomers of α -cyclo-dipolymethylenedithiophenes; that is, isomers with eclipsed and staggered sulfur atoms due to restricted rotation of the heterocyclic rings with short polymethylene chains. Finally, Raney nickel desulfurization⁴ of α -cyclo-dipolymethylenedithiophenes and their ring substituted derivatives would yield cyclic and substituted cyclic polymethylenes.

While the work described here was in progress a Russian paper reported⁵ the synthesis of several cyclic thiophene derivatives. These were reported,



without experimental details, analysis or structure proof, to have been prepared by the high dilution intramolecular Friedel-Crafts reactions of ω -(2-thienyl)-alkanoyl chlorides and the high dilution intermolecular acyloin condensation of 2,5-bis(ω -carbomethoxybutyl)thiophenes. More recently Winberg⁶ and his collaborators reported the preparation of the heterocyclophane, α -dicyclothiophene, in trace amounts, by the pyrolysis of 5-methyl-2-thienyltrimethylammonium hydroxide. The work reported here is concerned with the preparation and the attempted high dilution intramolecular condensations of four α, ω -bis[5'-(ω -carbomethoxyalkyl)-2'-thienyl]alkanes; diesters derived from either bis(2'-thienyl)methane (XVIII) or 1,6-bis(2'-thienyl)hexane (VI).

The intermediate diesters derived in turn from 1,4-bis(2'-thenoyl)butane (V) and 1,6-bis(2'-thienyl)hexane (VI) were obtained either by the diacylation of VI with an ω -carboalkoxyalkanoyl chloride or by the acylation of ethyl β -(2-thienyl)propionate with adipyl chloride as summarized in Chart I. The physical constants and analyses of the compounds involved are shown in Table I.

(4) H. Wynberg and A. Logothetis, *J. Am. Chem. Soc.*, **78**, 1958 (1956).

(5) Ya. L. Gol'dfarb, S. Z. Taiuts, and L. I. Belen'kii, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 1262 (1957); *Chem. Abstr.*, **52**, 6310 (1958).

(6) H. E. Winberg, F. S. Fawcett, N. E. Mochel, and C. W. Theobald, *J. Am. Chem. Soc.*, **82**, 1428 (1960).

Typical laboratory procedures employed are given in the Experimental. In some cases intermediates were not characterized but were used directly in the following step in the sequence of reactions. In an attempt to prepare 1,6-bis[5'-(γ -carboxypropyl)-2'-thienyl]hexane (IX) by an alternate route, 1,6-bis(2'-thienyl)hexane was converted to 1,6-bis(5'-formyl-2'-thienyl)hexane (XV). This dialdehyde could not be converted, by condensation with diethyl malonate, hydrolysis, and decarboxylation to 1,6-bis[5'-(γ -carboxypropenyl)-2'-thienyl]hexane, whose reduction would have yielded IX.

Compound VI was diacylated with propionic anhydride and 85% orthophosphoric acid to give 1,6-bis(5'-propionyl-2'-thienyl)hexane (XIII). Compound XIII was reduced using the modified Wolff-Kishner⁷ to the hydrocarbon 1,6-bis(5'-propyl-2'-thienyl)hexane (XIV). The latter was to be used for spectral comparisons with the α -cyclo-dipolymethylenedithiophenes (II). The ethyl β -(2-thienyl)propionate (XVII) was synthesized from thiophene *via* the 2-thenal⁸ and β -(2-thienyl)acrylic acid.⁹ The acrylic acid was reduced with 3% sodium amalgam^{9a} to β -(2-thienyl)propionic acid which on esterification gave XVII. The ester XVII was also obtained directly, in fair yields, by the low pressure catalytic hydrogenation,¹⁰ 5% palladium on charcoal, of β -(2-thienyl)acrylic acid in ethanol containing a trace of concentrated sulfuric acid.

The diesters derived from bis(2'-thienyl)methane (XVIII) are summarized in Chart II and the physical properties of these compounds are shown in Table I. Both bis[5'-(β -carbomethoxypropionyl)-2'-thienyl]methane (XIX)¹¹ and bis[5'-(ω -carbomethoxyvaleroyl)-2'-thienyl]methane (XX)¹² have been recently reported in the literature. Bis(2'-thienyl)methane (XVIII) was monoacylated and diacylated using propionyl chloride and stannic chloride and diacylated using propionic anhydride and 85% orthophosphoric acid. Bis(5'-propionyl-2'-thienyl)methane (XXV) was reduced to the saturated hydrocarbon bis(5'- n -propyl-2'-thienyl)methane (XXVII) which was to be used as a model compound for spectral comparisons. 5'-Propionyl-2',2-diethienyl methane (XXVI) was identified by means of its oxime and 2,4-dinitrophenylhydrazone derivatives. A small quantity of 1,2-bis(2'-thienyl)ethane (XXVIII)¹³ was diacylated with β -carbomethoxypropionyl chloride¹⁴ and stannic chloride to give an excellent yield of bis-1,2-[5'-(β -carbo-

(7) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(8) E. Campaigne and W. L. Archer, *ibid.*, **75**, 989 (1953).

(9) (a) G. Barger and A. Easson, *J. Chem. Soc.*, 2100 (1938); (b) W. J. King and F. F. Nord, *J. Org. Chem.*, **14**, 405 (1949).

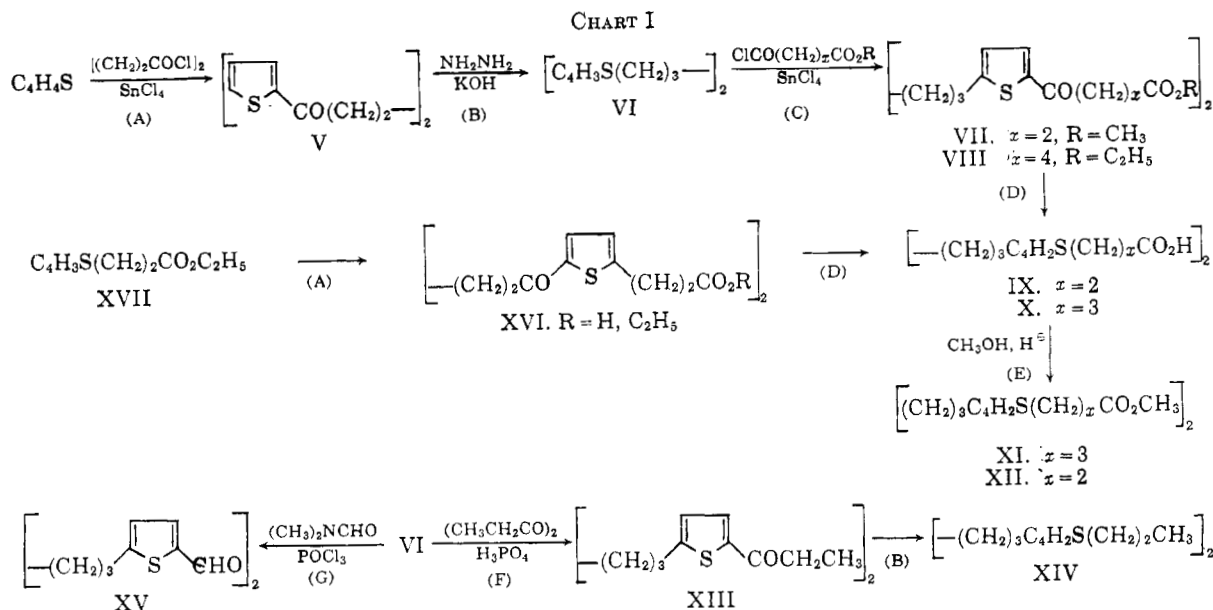
(10) P. Cogniant and D. Cogniant, *Bull. soc. chim. France*, **21**, 1349 (1954).

(11) Ya. L. Gol'dfarb and M. L. Kimalova, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 479 (1957); *Chem. Abstr.*, **51**, 15490 (1957).

(12) Ya. L. Gol'dfarb and M. L. Kimalova, *Izv. Akad. SSSR, Otdel. Khim. Nauk*, 570 (1955); *Chem. Abstr.*, **50**, 6422 (1956).

(13) F. F. Blicke and J. H. Burekhalter, *J. Am. Chem. Soc.*, **64**, 480 (1942).

(14) J. Cason, "Organic Synthesis," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 169.



Compound	Prep. proc.	Yield, %	M.p., °C.	B.p., °C.	Mm.	n_D^{20}	Formula	Carbon, %		Hydrogen, %		Sulfur, %	
								Calcd.	Found	Calcd.	Found	Calcd.	Found
V	A	85.5	126-127 ^a				C ₁₄ H ₁₄ O ₂ S ₂	60.40	60.08	5.07	4.98	23.03	22.80
XVI ^a	A	74.3	104.5-105 ^a				C ₂₄ H ₃₀ O ₆ S ₂	60.23	60.23	6.32	6.60	13.40	13.54
XVI ^b	B	55	200-202 ^a				C ₂₀ H ₂₂ O ₆ S ₂	56.85	57.24	5.25	5.71	15.18	14.80
VI	B	70		118-120	0.06	1.5599	C ₁₄ H ₁₆ S ₂	67.15	67.36	7.24	7.18	25.61	25.64
XIV	B	71		162-165	.06	1.5319	C ₂₀ H ₃₀ S ₂	71.79	71.58	9.04	8.86	19.17	19.29
XXVII	B	37.5		115-120	.07	1.5523	C ₁₅ H ₂₀ S ₂	68.13	68.12	7.62	7.68	24.25	24.20
VII	C	70	90-91 ^a				C ₂₄ H ₃₀ O ₆ S ₂	60.23	59.95	6.32	6.29	13.40	13.26
VIII	C	69	69-70 ^a				C ₃₀ H ₄₂ O ₆ S ₂	64.02	64.18	7.52	7.70	11.39	11.67
XXIX	C	76.8	118-119.5 ^a				C ₂₀ H ₂₂ O ₆ S ₂	56.85	57.06	5.25	5.33	15.18	15.23
XX	C	45.7	84-85.5 ^a				C ₂₅ H ₃₂ O ₆ S ₂	60.95	61.02	6.55	6.63	13.02	12.98
IX	D	100	166-167 ^a				C ₂₀ H ₂₅ O ₆ S ₂	60.88	60.76	6.64	6.62	16.25	16.05
XXII	D	84.3	91-92 ^b				C ₂₁ H ₂₈ O ₄ S ₂	61.72	61.76	6.91	6.97	15.69	15.75
XI	E	67.8		260-264	.1	1.5282	C ₂₄ H ₃₄ O ₄ S ₂	63.96	63.67	7.60	7.52	14.23	14.32
XII	E	74	53-54 ^a				C ₂₂ H ₃₀ O ₄ S ₂	62.52	62.43	7.16	7.11	15.17	15.20
XXIII	E	68.3		203-205	.06	1.5418	C ₁₉ H ₂₄ O ₄ S ₂	59.97	59.63	6.36	6.24	16.85	16.84
XXIV	E	70.5		240-244	.4	1.5310	C ₂₃ H ₃₂ O ₄ S ₂	63.27	62.73	7.39	7.10	14.69	14.81
XIII	F	89.5	88.5-89.5 ^a				C ₂₀ H ₂₆ O ₂ S ₂	66.26	66.45	7.23	7.18	17.69	17.90
XXV	F	56.5	100.5-101.5 ^a				C ₁₅ H ₁₆ O ₂ S ₂	61.61	61.74	5.52	5.43	21.93	22.07
XXVI oxime	F		98.5-99.5 ^a				C ₁₂ H ₁₃ NOS ₂	57.34	57.47	5.21	5.35		
XXVI ^c DNPH ^d	F		154-155 ^c				C ₁₅ H ₁₆ N ₂ O ₄ S	51.91	52.01	3.87	4.07		
XV ^e	G	70	86-87 ^a				C ₁₆ H ₁₈ O ₂ S ₂	62.70	62.63	5.92	5.79	20.92	20.63
XXXI		32	72-74 ^a				C ₁₄ H ₁₄ O ₂ S ₂	60.41	60.54	5.07	5.13	23.04	22.84
XXXII ^e		78	94-95 ^a				C ₂₀ H ₁₈ N ₂ S ₂	68.54	68.50	5.17	5.21	18.30	18.31

Solvents of recrystallization: ^a Ethanol; ^b Ethanol-water; ^c Ethyl acetate; ^d DPNH = 2,4-dinitrophenylhydrazone; ^e Nitrogen, % Calcd., Found, XXVI 5.57, 5.41, XXVII 13.45, 13.56; XXXII 7.99, 7.95.

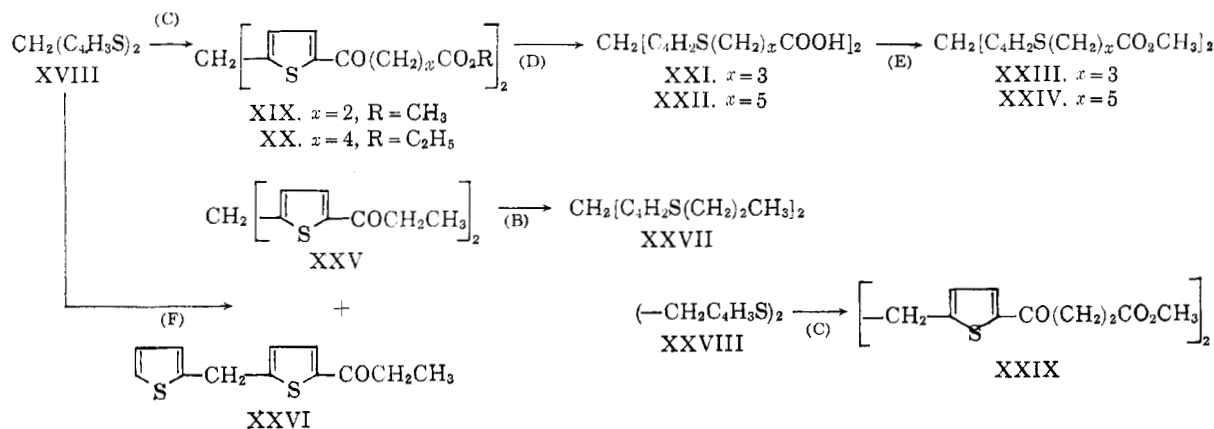
methoxypropionyl) - 2' - thienyl]ethane (XXIX). This sequence of reactions was not investigated further due to the unsuccessful cyclization results obtained. It is interesting to note that the diacyla-

tion reactions with VI and XXVIII resulted in relatively good yields of an easily purified product while the diacylation of XVIII gave low yields of a product which was very difficult to obtain in a

reasonably pure state. The bis(2'-thienyl)methane was synthesized by a Friedel-Crafts acylation of thiophene with thienyl chloride¹⁶ followed by a Wolff-Kishner reduction of the dithenyl ketone.

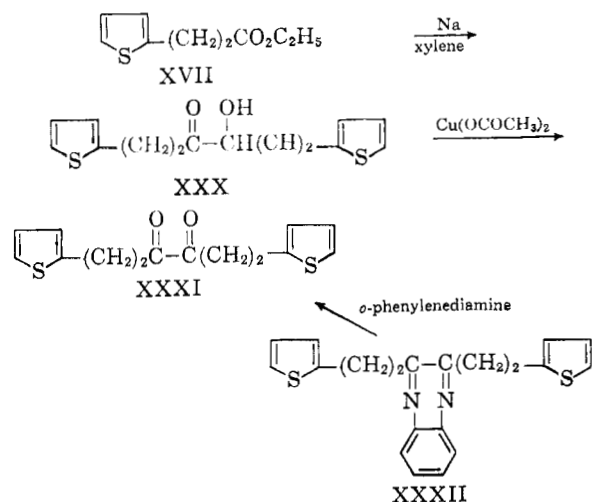
conditions (a vigorously stirred, refluxing suspension of sodium in xylene, in an oxygen-free nitrogen atmosphere) ethyl β -(2-thienyl)propionate (XVII) gave 100% of an intracable polymeric material at

CHART II



The high dilution intramolecular acyloin condensations were carried out following modified experimental procedures of Cram¹⁶ and Blomquist¹⁷ in their successful paracyclophane syntheses. Several attempts to cyclize the diesters, XII and XXIII, yielded only recovered starting diesters (78 and 91%, respectively) as evidenced by melting point or boiling point, index of refraction, mixed melting points, infrared spectra, and a negative acyloin test.¹⁸ To verify the soundness of the experimental conditions and apparatus being used, diethyl sebacate was prepared and easily cyclized to sebacoin (40%).¹⁹ Under the same experimental

room temperature. However, the linear acyloin, 3-hydroxy-4-keto-1,6-bis(2'-thienyl)hexane (XXX) was synthesized in a 38.1% yield at a reaction temperature of 60–70°. This result indicated that the thiophene ring *per se* does not prevent the linear acyloin reaction of a thiophene ester. The crude linear acyloin XXX was oxidized to the diketone, XXXI, with copper acetate,²⁰ and the diketone compound was converted to its quinoxaline derivative. However, when the diester XII was subjected to the lower reaction temperature conditions which had yielded the linear acyloin (XXX) only starting material was recovered (96.2%). The use of longer addition periods of the diester to the sodium xylene or of a 50% excess of sodium, only increased the amount of polymeric material at the expense of recovered starting ester, and failed to yield any of the desired cyclic acyloin.



(15) N. P. Buu-Hoi, M. Michal, and N. D. Zuong, *Bull. soc. chim. France*, **22**, 1853 (1955).

(16) D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, **73**, 5691 (1951).

(17) A. T. Blomquist and F. Jaffe, *ibid.*, **80**, 3405 (1958).

(18) W. Rigby, *J. Chem. Soc.*, 793 (1951).

(19) N. I. Allinger, *Org. Syn.*, **36**, 79 (1956).

An examination of molecular models of the diesters and the corresponding acyloins indicated that with the exception of XXIII ($n=1$, $x=3$) which formed a model cyclic acyloin with difficulty, all the other diesters, XI, XII, and XXIV, prepared in this study should or could form the cyclic acyloins readily. Further attempts to bring about the cyclic acyloin ring closure by variation in the quantity of ester used, volume of solvent, reaction time, and temperature failed. In addition, an attempt to apply a modification of Leonard's²¹ high dilution Dieckmann cyclization method to the cyclization of the diester XII yielded only an intraceable polymeric material. At present no satisfactory explanation can be offered for the failure of the cyclic acyloin condensations of the α,ω -bis-5'-(ω -carboalkoxyalkyl)-2'-thienylalkanes.

(20) A. T. Blomquist and A. Goldstein, *Org. Syn.*, **36**, 77 (1956).

(21) N. J. Leonard and C. W. Schimpfening, Jr., *J. Org. Chem.*, **23**, 1708 (1958).

Experimental²²

Procedure A. 1,4-Bis(2'-thenoyl)butane (V).—A mixture of 18.3 g. (0.1 mole) adipyl chloride,²³ 35 ml (0.44 mole) of thiophene, and 150 ml. of benzene or ethylene dichloride was cooled to -3° . To the chilled, stirred mixture, anhydrous stannic chloride (59 g., 0.225 mole) was added at a rate to maintain the reaction temperature below 0° . Following the addition of the metal chloride, the dark red mixture was stirred at room temperature for 1 hr., and poured over ice and hydrochloric acid with vigorous stirring. The diketone was extracted with hot benzene if the latter was used as the reaction media or it was recovered by filtration when ethylene dichloride was the reaction solvent. It was recrystallized from either benzene (Norit) or ethanol (Norit) to yield 23.8 g. (0.0855 mole, 85.5%) of almost white needles, m.p. $125-127^{\circ}$. An analytical sample was recrystallized twice from ethanol (Norit), m.p. $126-127^{\circ}$.

Procedure B. 1,6-Bis(2'-thienyl)hexane (VI).—A 62-g. quantity (0.22 mole) of 1,4-bis(2'-thenoyl)butane dissolved in 350 ml. of diethylene glycol was reduced using 82 g. (1.47 moles) of potassium hydroxide and 75 ml. of 85% hydrazine hydrate. The reactants were initially refluxed for 2 hr. Excess hydrazine and water were removed by distillation until the reaction flask temperature reached $195-200^{\circ}$. Reduction was completed by keeping the reaction mixture at this temperature for 5 hr. It was then cooled, diluted with water (1 l.), and extracted with three 100-ml. fractions of ether. These were combined, washed with water, and dried. After removal of the ether, distillation of the residue yielded 38.5 g. (0.154 mole, 70%) of the hydrocarbon (VI), b.p. $140-144^{\circ}$ (0.75 mm.). Redistillation of a middle fraction gave a colorless liquid boiling $118-120^{\circ}$ (0.06 mm.).

Procedure C. 1,6-Bis[5'-(α -carbomethoxypropionyl)-2'-thienyl]hexane (VII).—To 50 g. (0.2 mole) of 1,6-bis(2'-thienyl)hexane and 60 g. (0.4 mole) of β -carbomethoxypropionyl chloride,¹⁴ dissolved in 200 ml. of ethylene dichloride held at -5° , was added slowly 104 g. (0.4 mole) of anhydrous stannic chloride. The dark-colored reaction mixture was stirred for 1 hr. at room temperature and then hydrolyzed by pouring it onto ice and hydrochloric acid. The keto ester was recovered by filtration and yielded, after two recrystallizations from ethanol (Norit), 67 g. (0.14 mole, 70%) of colorless platelets, m.p. $88-90^{\circ}$. The analytical sample was recrystallized three times from ethanol (Norit), m.p. $90-91^{\circ}$.

Procedure D. 1,6-Bis[5'-(β -carboxyethyl)-2'-thienyl]hexane (IX).—This material was prepared by the modified Wolff-Kishner reduction of 138 g. (0.238 mole) of 1,4-bis[5'-(β -carbomethoxyethyl)-2'-thenoyl]butane (XVI). This was affected by refluxing it with 150 ml. of 85% hydrazine hydrate and 150 g. (2.68 mole) of potassium hydroxide dissolved in 600 ml. of diethylene glycol for 1 hr. Excess hydrazine hydrate and water were removed by distillation until the flask temperature reached $190-200^{\circ}$, at which temperature it was kept for an additional 5 hr. Dilution of the reaction mixture with water, and acidification with concentrated hydrochloric acid gave 13.5 g. (0.288 mole, 100%) of IX, m.p. $162-166^{\circ}$. An analytical sample after two recrystallizations from ethanol (Norit) melted at $166-167^{\circ}$.

Procedure E. 1,6-Bis[5'-(β -carbomethoxyethyl)-2'-thienyl]hexane (XII).—A 90-g. quantity (0.213 mole, 74%) of this ester, m.p. $53-54^{\circ}$, was obtained by refluxing a mixture of 113 g. (0.288 mole) of 1,6-bis[5'-(β -carboxyethyl)-2'-thienyl]hexane and 300 ml. (7.4 moles) of absolute methanol catalyzed with 5 ml. of concentrated sulfuric acid for 20 hr. The ester was isolated by dilution of the reaction mixture with water and recovery of the solid diester by filtration. An

analytical sample was obtained, in the form of heavy, colorless platelets (m.p. $53.5-54.5^{\circ}$), by recrystallization from ethanol (Norit).

Procedure F. 1,6-Bis(5'-propionyl-2'-thienyl)hexane (XIII).—A mixture of 12.5 g. (0.05 mole) of 1,6-bis(2'-thienyl)hexane, 15.6 g. (0.12 mole) of propionic anhydride, and 1.2 g. of 85% orthophosphoric acid,¹¹ as the catalyst, was refluxed for 3 hr. and poured into 100 ml. of water. A yellow-brown solid separated. This was recovered by filtration, washed with aqueous sodium carbonate, dried, and recrystallized twice from ethanol (Norit) to yield 18.1 g. (0.0447 mole, 89.5%) of colorless platelets, m.p. $87-89^{\circ}$. After four recrystallizations from ethanol, an analytical sample melted at $88.5-89.5^{\circ}$.

Procedure G. 1,6-Bis(5'-formyl-2'-thienyl)hexane (XV).—To 8.7 g. (0.035 mole) of 1,6-bis(2'-thienyl)hexane and 6.4 g. (0.087 mole) of dimethylformamide was added 13.3 g. (0.087 mole) of phosphorus oxychloride. After heating the reaction mixture (steam bath) for 1 hr., it was poured onto ice and neutralized with sodium carbonate. The yield of dialdehyde after recrystallization from ethanol (Norit) was 7.5 g. (0.0245 mole, 70%) of a yellow-colored solid, m.p. $85-86^{\circ}$. An analytical sample obtained by two recrystallizations from ethanol melted at $86-87^{\circ}$.

3-Hydroxy-4-keto-1,6-bis(2'-thienyl)hexane (XXX).—To a suspension, agitated with a high-speed stirrer and containing 8.5 g. (0.37 g.-atom) of sodium sand dispersed in 150 ml. of xylene under an oxygen-free nitrogen atmosphere maintained by passing a steady flow of the latter through the apparatus during the reaction, was slowly added from a Hershburg dropping funnel during 0.75 hr., 33 g. (0.179 mole) of ethyl β -(2-thienyl)propionate, dissolved in 100 ml. of xylene. The reaction mixture was held at $60-70^{\circ}$, during the addition of the ester, then refluxed for 0.25 hr. during which it changed from an initial gray through red to orange and finally to a brown color. After cooling the reaction mixture first with an air stream, then in water, and finally in an ice bath, a solution of 40 ml. of glacial acetic acid dissolved in 40 ml. of xylene was added to it, precipitating a red-paste which rapidly turned white. The addition of 100 ml. of water dissolved the white pasty material and caused the separation from solution of a yellow layer. Filtration of the two phase mixture yielded no polymeric material.

The aqueous layer was separated and extracted with 50 ml. of xylene. The combined xylene fractions were washed four times with 50-ml. portions of water and dried over anhydrous sodium sulfate. Removal of the xylene yielded a yellow liquid with a rather disagreeable odor. This was vacuum distilled and seven fractions were collected, boiling in the temperature range $165-181^{\circ}$, with the major amount of the material boiling in the range $177-181^{\circ}$. All the fractions collected gave a positive acyloin test. The total weight of the crude acyloin was 19.1 g. (0.068 mole, 38.1%).

Since attempts to prepare both *p*-nitrobenzoate and urethan derivatives of this product were unsuccessful, the crude acyloin was oxidized to the diketone with cupric acetate.²⁰ A well stirred mixture of 2.8 g. (0.01 mole) of the crude acyloin and 4 g. (0.02 mole) of cupric acetate monohydrate dissolved in 50 ml. of 50% aqueous acetic acid was heated cautiously with an open flame of a microburner for 5 min. This showed no color change in the reaction mixture, while sebaccin, under the same conditions, forms a red precipitate in a few minutes. The reaction solution was filtered with Celite on a sintered glass funnel and the filter cake was washed with ether until a fresh 10-ml. portion of ether filtrate no longer was brown. The green aqueous layer was extracted with the ether filtrate used in the washings, which caused the aqueous layer to take on a blue coloration. The combined ether extracts, 90-100 ml., were washed twice with 25 ml. of saturated salt solution, then with 10% sodium carbonate until neutral, and again with 50 ml. of saturated sodium chloride solution.

The ether solution was dried with sodium sulfate and the ether removed to leave a red solid residue which on re-

(22) Analyses by Micro-Tech Laboratories, Skokie, Illinois. The melting points and boiling points are uncorrected.

(23) R. C. Fuson and J. T. Walker, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 169 (1955).

crystallization from ethanol (Norit) yielded 0.9 g. (0.0032 mole, 32%) of a bright yellow product as plates, m.p. 72–74°.

The diketone was converted to its quinoxaline derivative by refluxing, for an hr., 0.3 g. (0.0011 mole) of it with 0.25 g. (0.0023 mole) of freshly recrystallized *o*-phenylenediamine in 18 ml. of glacial acetic acid. The derivative was isolated by pouring the reaction mixture into 30 ml. of water and cooling to 0°. It was recovered, by filtration, dried, and recrystallized from ethanol (Norit) to give 0.3 g. (8.6 × 10⁻⁴ mole, 78%) of colorless needles, m.p. 94–95°.

Attempted Intramolecular Acyloin Condensations.—The acyloin condensations were carried out using the apparatus and modifications of the procedures described by Cram¹⁶ and Blomquist.¹⁷ During a 14-hr. period, 42.2 g. (0.1 mole) of 1,6-bis[5'-(β-carbomethoxyethyl)-2'-thienyl]hexane dissolved in 400 ml. of xylene was added to a stirred suspension of 9.5 g. (0.41 g.-atom) of sodium in 300 ml. of refluxing xylene. The reaction mixture was heated for a short period following the addition of the diester, then cooled and a mixture of 100 ml. of glacial acetic acid and 100 ml. of xylene was added which precipitated sodium acetate. A 200-ml. volume of water was added to dissolve the sodium acetate and separate the reaction mixture into two phases, which on filtration yielded 3.8 g. (ca. 9%) of a polymeric material.

The aqueous layer was separated and extracted with 100 ml. of xylene. The combined extract and organic layer were washed four times with water and dried. Removal of the solvent yielded a light brown residue which solidified on cooling. Recrystallization of the solid from methanol (Norit) gave 29 g. of the starting diester, m.p. 52–54°. Additional quantities of unchanged diester were obtained from the mother liquors to give a combined weight of 32.8 g. (0.078 mole, 78%) of recovered diester.

Attempted Intramolecular Dieckmann Cyclization of 1,6-

Bis[5'-(β-carbomethoxyethyl)-2'-thienyl]hexane.—Using a modification of Leonard's procedure²¹ of the intramolecular Dieckmann cyclizations, 250 ml. of dry xylene and 45 g. (0.61 mole) of *t*-butyl alcohol were put in a 3 l. creased flask and 9.3 g. (0.24 g.-atom) of potassium metal (cut in small chunks) were added to the mixture. When the metal had reacted, excess *t*-butyl alcohol was removed and 22 g. (0.05 mole) of the diester dissolved in 200 ml. of xylene was added during 5 hr. The reaction mixture was then heated for a short period, cooled, and 60 ml. of glacial acetic acid and 30 ml. of xylene were added to it, precipitating a white solid. After adding 200 ml. of water to the acidified reaction mixture, 9.1 g. (about 41%) of a polymeric material was collected on filtration of the two phase mixture. The polymer was insoluble in benzene, chloroform, ether, acetone, ethylene dichloride, ethyl acetate, and methylene dichloride and only partially soluble in dimethylformamide.

The xylene layer was separated from the filtrate and the aqueous layer was extracted with 50 ml. of xylene. The extract and xylene layer were combined, washed with water, and dried. Removal of the xylene yielded a brown, oily liquid. This was refluxed with 20 ml. of 3 *N* hydrochloric acid and 5 ml. of ethanol for 12 hr. which caused the evolution of carbon dioxide, observed by precipitation of barium carbonate. The cool hydrolysis mixture was extracted twice with ether in which it was not completely soluble. Removal of the ether left a gummy brown residue which was dissolved in ethyl acetate and decolorized with Norit. The addition of hexane reprecipitated the brown material as an oil which failed to form a crystalline 2,4-dinitrophenylhydrazone.

The ether-insoluble material was dissolved in 50 ml. of methylene dichloride, washed with 25 ml. of water, and dried with anhydrous magnesium sulfate. After removal of the solvent, low pressure distillation (1.0 mm.) of the residue resulted only in its thermal decomposition.

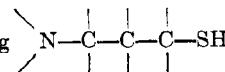
Addition of Hydrogen Sulfide to Unsaturated Amines

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Thiolation of *N*-alkenyl compounds with hydrogen sulfide was investigated as a means of obtaining



structures in connection with the synthesis of potential antiradiation drugs. Irradiating allylamine and hydrogen sulfide gave essentially no thiolation. Heating a mixture of allylamine and hydrogen sulfide, with a free-radical-generating agent, gave a mixture, with Markownikoff addition the predominant reaction. With allylamine hydrochloride and ultraviolet irradiation thiolation resulted, and the mode of addition was directed exclusively to the anti-Markownikoff product, 3-amino-1-propanethiol. Several 3-amino-1-alkanethiols were prepared in this manner. 3-Mercaptopropylformamide and *N*-(3-mercaptopropyl)succinimide were also prepared by this terminal thiolation reaction. The reactivity of *N*-allyl compounds was apparently influenced by electron density at the nitrogen atom, with the observed order of reactivity being imide > amine hydrochloride > amide > dialkylamine hydrochloride > amine acetate >> amine. With 3-aminocyclohexene hydrochloride (nonterminal double bond), the products isolated were *cis*- and *trans*-2-aminocyclohexanethiol. Similarly, 1-amino-2-butanethiol was obtained from 1-amino-2-butene hydrochloride. Reaction of *N*-vinyl-2-pyrrolidone with hydrogen sulfide, using ultraviolet light, gave *N*-2-mercaptoethyl-2-pyrrolidone in good yield. *N*-2-Mercaptoethylcaprolactam was prepared in a similar manner.

Compounds containing both amine and thiol groups, and related derivatives, are being investigated extensively as protectants against the harmful effects of ionizing radiation.^{1,2} As participants in a program of synthesis of potential antiradiation

drugs of this type,³ an initial task in these laboratories was the preparation of a kilogram lot of high purity 3-amino-1-propanethiol hydrochloride and homologs of the type H₂NCH(R)CH₂CH₂SH (R = alkyl). The parent compound, 3-amino-1-propanethiol, was described in the early literature by

(1) D. R. Kalkwarf, *Nucleonics*, **18**, No. 5, 76 (1960) (review and bibliography).

(2) *Chem. Eng. News*, p. 42, Nov. 23 (1959).

(3) This work was done under Contract DA-49-193-MD-2069 with U. S. Army Medical Research and Development Command.