Thiaindanones

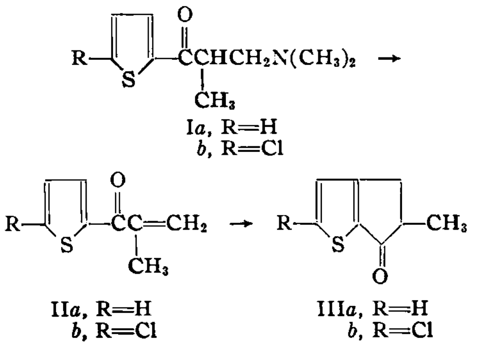
Thiophene Isosteres of Indanone

By JOSEPH SAM and ALONZO C. THOMPSON

The preparation of substituted 4- and 6-thiaindanones[1] (thiophene isosteres of indanone) *via* intramolecular acylation of β-(2- and 3-thienyl)propanoic acids is described. The Wolff-Kishner and sodium borohydride reductions provided the corresponding thiaindan and thiaindanol (thiophene isosteres of indan and indanol), respectively.

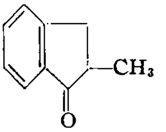
THE IMPORTANCE of molecular size and shape in determining biological properties has been recognized for many years. The chemical, physical, and biological properties of isosteres have been studied extensively (2), since they possess steric similarities. Interest in the synthesis and in the biological properties of isosteres is kindled in the hope that useful medicinal agents and essential clues to the mechanism of drug action may be obtained.

Burckhalter and Sam (1) prepared the thiophene isostere (III*a*) of 2-methyl-1-indanone (IV) but did not report biological activity. Since the thiaindanones (III) represented a ring system that had not been investigated extensively, we were interested in the preparation of other thiophene isosteres of indanone and in ascertaining their biological properties. Moreover, since the presence of the sulfur atom gives rise to an unsymmetrical molecule, we were also interested in the preparation of the isomeric thiophene isosteres (V). During the course of our work Poirier (3) described the preparation of some closely related derivatives of this ring system.


I*a*, R=H
b, R=Cl

II*a*, R=H
b, R=Cl

III*a*, R=H
b, R=Cl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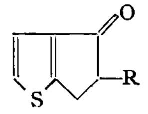
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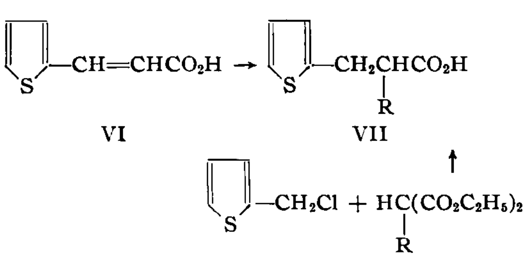
The method (I→III) reported by Burckhalter and Sam (1) for the preparation of III*a* is not generally applicable to other substituted thiaindanones. Except for the preparation of the chloro derivative (III*b*) we made use of the intramolecular acylation of substituted β-thienylpropanoic acids. The substituted β-(2-thienyl)propanoic acids (VII) were prepared by the condensation of 2-thenyl chloride with substituted malonates according to the procedure described by Levy (4) and modified by Sam and Plampin (5) for the preparation of substituted hydrocinnamic acids. The unsubstituted acid (VII, R=H) was obtained from the reduction of the corresponding acrylic acid (VI)


VI VII

The reduction of VI was accomplished either with 10% sodium-lead alloy in water at room temperature or catalytically at 3–4 Atm. with 10% palladium-on-charcoal catalyst. Contrary to expected results, we obtained a good yield in the catalytic reduction of VI to VII (R=H).

The substituted β-(3-thienyl)propanoic acids (VIII) were prepared from 3-thenyl bromide *via* condensation with substituted malonates (6)

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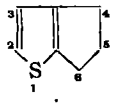
[1] Because of the cumbersome chemical name originally assigned (1) to III*a*, *i.e.*, 4,5-dihydro-5-methyl-6H-cyclopenta-(b)thiophen-6-one, we propose the name thiaindan for the thiophene isostere (i) of indan (ii), and the names thiaindanone and thiaindanol for the corresponding isosteres of indanone and indanol, respectively.



i

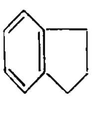

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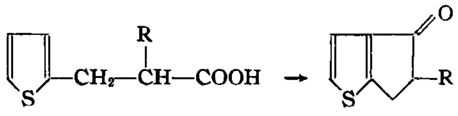
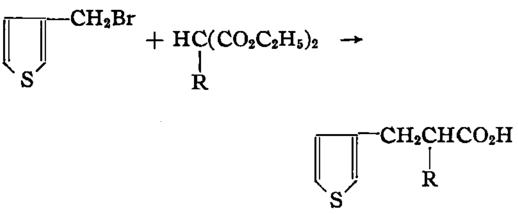
TABLE I.—THIAINDAN-4-ONES



VII V

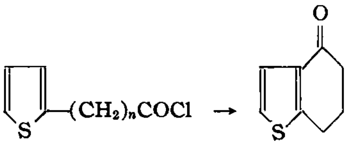
R	Solvent for VII	Reaction Temp., °C.	Reaction Time, hr.	Yield, %	Cyclization Agent
CH$_3$	C$_6$H$_5$Cl	130	0.25	54	PPA[a]
CH$_3$	C$_6$H$_5$Cl	120	0.25	48	PPA
CH$_3$	...	120	0.25	36	PPA
CH$_3$	C$_6$H$_5$Cl	115	0.25	37	PPA
CH$_3$	...	30–80[b]	0.25–12[b]	0	PPA
CH$_3$[c]	CS$_2$	...	0.5	0	AlCl$_3$
CH$_3$[c]	CS$_2$	...	2	0	AlCl$_3$
CH$_3$[c]	CS$_2$	...	2	0	SnCl$_4$
CH$_3$	...	30, 45	0.75	0	H$_2$SO$_4$
CH$_3$	...	30	12	0	HF
H	CH$_2$Cl$_2$	120	0.25	36	PPA
C$_6$H$_5$	C$_6$H$_5$Cl	115	0.25	16	PPA
H	...	30	12	0	HF
C$_6$H$_5$	...	30	12	0	HF

[a] Polyphosphoric acid. [b] Eight separate experiments varying the temperature and duration. [c] Acid chloride.



VIII

Intramolecular acylation studies of the substituted β-(2 and 3-thienyl)propanoic acids are summarized in Tables I and II. Our studies (Table I) with α-methyl-β-(2-thienyl)propanoic acid revealed that a solution of the organic acid in chlorobenzene when added to polyphosphoric acid (PPA) at an elevated temperature (preferably 130°) over a short period of time gave the best results. The use of other dehydrating agents such as sulfuric acid and liquid hydrogen fluoride gave negligible results. In contrast to the good results obtained by Fieser and Kennelly (7) with the cyclization of γ-(2-thienyl)butanoyl chloride (IX, $n = 3$) to X, we were unable to cyclize β-(2-thienyl)propanoyl chloride (IX, $n = 2$) to V (R = H) utilizing the same conditions. Aluminum chloride also was ineffective in the cyclization of the acid chloride

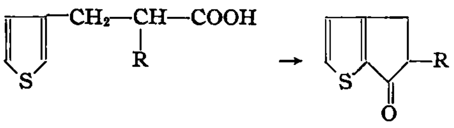


IX X

The intramolecular acylation of substituted β-(3-thienyl)propanoic acids (VIII) to the corresponding substituted 6-thiaindanones (XI, Table II) was accomplished without difficulty and in moderate yields with either PPA or liquid hydrogen fluoride. In contrast to the sluggish cyclization of the isomeric 2-thienyl acids (VII), the ease with which this cyclization was accomplished is explained on the basis of the differences in the reactivity of the 2 and 3 positions of thiophene.

The 5-methyl-6-thiaindanone, III*a*, undergoes

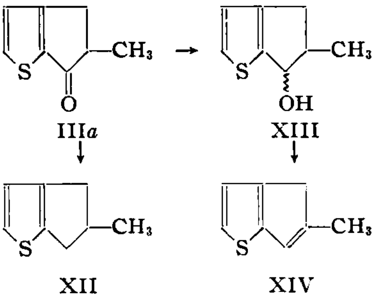
TABLE II.—THIAINDAN-6-ONES



VIII XI

R	Solvent for VIII	Reaction Temp., °C.	Reaction Time	Yield, %	Cyclization Agent
H	C$_6$H$_5$Cl	75	5 min.	10.4	PPA
H	...	30	12 hr.	43.9	HF
ϕ	C$_6$H$_5$Cl	130	15 min.	21.7	PPA
ϕ	...	30	48 hr.	71.9	HF
CH$_3$	C$_6$H$_5$Cl	70	1 hr.	60.0	PPA
CH$_3$	...	70	1 hr.	0.0	PPA

the typical Wolff-Kishner reduction (8) to give the thiophene isostere (XII) of 2-methylindan; sodium borohydride reduction (9) of III*a* yielded a thiophene isostere (XIII) of 2-methyl-1-indanol. Preliminary attempts to obtain the isomeric alcohol have been unsuccessful. Since analogous reductions of 2-methyl-1-indanone to 2-methyl-1-indanol with sodium borohydride have provided exclusively the *cis*-2-methyl-1-indanol, we believe the reduction of III*a* likewise gives the *cis* isomer.



The dehydration of 5-methyl-6-thiaindanol occurred on heating and resulted in a product (XIV?) which gave the characteristic tests for unsaturation. However, this material rapidly deteriorated and was not fully characterized.

Preliminary pharmacological studies in mice demonstrated that the semicarbazones of III*a* and V (R = CH_3) exhibit weak anticonvulsant activity. The acid, VIII (R = CH_3), and the ketone, XI (R = H), also exhibited weak anticonvulsant activity. The semicarbazone of III*a* produced a weak antihypertensive response in both rats and dogs.

EXPERIMENTAL[2]

β-(2-Thienyl)propanoic Acid.—*Method A*.—A 9.6% lead-sodium alloy (100 Gm.) was added to a stirred solution of 15.4 Gm. (0.1 mole) of β-(2-thienyl)acrylic acid in 200 ml. of 10% sodium hydroxide solution over a period of 2 hours. The mixture was filtered and the basic filtrate neutralized with concentrated hydrochloric acid. The precipitate was removed by filtration, air dried, and recrystallized from petroleum ether (b.p. 30–60°) to give 10 Gm. (64%) of product, m.p. 48–49° (lit. (10) m.p. 46–48°).

Method B.—A solution of 15.4 Gm. (0.1 mole) of β-(2-thienyl)acrylic acid in 200 ml. of methanol was treated with 2 Gm. of 10% palladium-carbon catalyst and hydrogenated at 42 p.s.i. Hydrogenation was complete at the end of 1 hour; no further hydrogen uptake occurred during an additional hour. The catalyst was removed by filtration and the solvent was distilled *in vacuo* leaving 12.6 Gm. (80%) of product, m.p. 48–49°. The infrared spectra of samples from *Methods A* and *B* were identical. Mixed melting points showed no depression.

α-(Methyl-β-(3-thienyl)propanoic Acid.—To a solution of 234.6 Gm. (1.4 moles) of diethyl methylmalonate in ethanolic sodium ethoxide (made from 29.7 Gm. (1.3 Gm. At.) of sodium and 600 ml. of ethanol) was added through a dropping funnel 230 Gm. (1.3 moles) of 3-thenyl bromide and the mixture heated at reflux for 7 hours. A solution of 300 Gm. (5.36 moles) of potassium hydroxide in 300 ml. of water was added to the ethanol solution and the mixture refluxed for 24 hours. The mixture was concentrated *in vacuo* to about 400 ml. The residual mixture was treated with 500 ml. of water, cooled in an ice bath, neutralized with concentrated hydrochloric acid, and extracted with ether. Evaporation of the ether and distillation of the residual oil gave 151 Gm. of product (68%), b.p. 141–145° (5 mm.) n_D^{28} 1.5225.

Anal.—Calcd. for $C_8H_{10}O_2S$: C, 56.5; H, 5.9. Found: C, 56.4; H, 6.2.

The amide was prepared in the usual manner and recrystallized from an ethanol-water mixture and water, respectively, m.p. 121–122°.

Anal.—Calcd. for $C_8H_{11}NOS$: C, 56.8; H, 6.5. Found: C, 57.0; H, 6.8.

α-Phenyl-β-(3-thienyl)propanoic Acid.—The procedure for the synthesis of α-methyl-β-(3-thienyl)-propanoic acid was employed using 177 Gm. (1.0 mole) of 3-thenyl bromide and 238 Gm. (1.0 mole) of diethyl phenylmalonate. Ninety-seven grams (42%) of product were obtained, b.p. 194° (2.5 mm.); m.p. 87–89°.

The amide was prepared in the usual manner and recrystallized from an ethanol-water mixture, m.p. 130–132°.

Anal.—Calcd. for $C_{13}H_{13}NOS$: C, 67.5; H, 5.6; N, 6.1. Found: C, 67.6; H, 5.5; N, 6.0.

Cyclization of β-(2- and 3-Thienyl)propanoic Acids to Thiaindanones (Tables I, II). *Polyphosphoric Acid Method.*—The appropriate β-(2- and 3-thienyl)propanoic acid *per se* or dissolved in 100 ml. of solvent was added with stirring to 200 Gm. of polyphosphoric acid, preheated to the desired temperature. The dry acid was added essentially in one lot, whereas the solution of the acid in the solvent was added over a 15-minute period. Thereafter, the mixture was poured with stirring into 200 ml. of ice water. The mixture was extracted with either ethyl acetate or ether. The combined extracts were washed with water, 10% sodium bicarbonate solution, and dried over anhydrous sodium sulfate. Evaporation of the solvent and distillation or recrystallization of the residue provided the desired product (Table III). Infrared spectra in carbon tetrachloride showed strong carbonyl absorption at 1625–1740 cm.$^{-1}$

Hydrogen Fluoride Method.—The procedure was adapted from that of Heinzelmann and co-workers (11) for the cyclization of substituted phenylpropanoic acids. A 250-ml. copper retort containing 0.1 mole of the appropriate thienylpropanoic acid per 150 Gm. of liquid hydrogen fluoride was allowed to remain overnight in a fume hood. The contents of the retort were poured into a copper beaker and the remaining hydrogen fluoride evaporated. An ethereal solution of the residual material was washed with water and 10% sodium bicarbonate solution, respectively. The product was isolated as described above.

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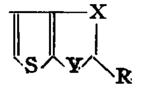
[2] All melting points were taken on a Fisher-Johns apparatus and are corrected; boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer model 137 infracord spectrophotometer.

TABLE III.



R	X	Y	M.p., °C.	B.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	CO	CH_2	115–117	110 (0.2 mm.)	C_7H_6OS	60.9	61.4	4.4	4.6	...	...
CH_3	CO	CH_2	39–40	88–98 (0.7 mm.)	C_8H_9NOS	...	...	...	...	...	...
CH_3	CO	CH_2	243–245[a]	...	$C_{14}H_{12}N_4O_4S$[b]	50.6	50.8	3.6	3.6	16.9	16.7
CH_3	CO	CH_2	121–122[c]	...	C_8H_9NOS[d,e]	57.5	57.7	5.4	5.3	8.4	8.3
CH_3	CO	CH_2	190–192[c]	...	$C_9H_{11}N_3OS$[f]	51.7	51.7	5.3	5.1	...	...
C_6H_5	CO	CH_2	103–104	185 (2 mm.)	$C_{13}H_{10}OS$	72.9	73.1	4.7	4.9	...	...
H	CH_2	CO	90–91	110 (7 mm.)	C_7H_6OS	60.0	61.1	4.3	4.4	...	...
CH_3	CH_2	CO	...	106 (2 mm.)	C_8H_9NOS[g]	...	...	...	...	...	...
CH_3	CH_2	CO	183–185[c]	...	$C_9H_{11}NO_3S$[f]	51.7	51.8	5.3	5.4	...	...
CH_3	CH_2	CO	121–123[c]	...	C_8H_9NOS[d]	57.5	57.4	5.4	5.8	...	...
C_6H_5	CH_2	CO	96–97[c]	180 (1 mm.)	$C_{13}H_{10}OS$[h]	72.9	73.0	4.6	4.7	...	...
CH_3	CH_2	CO	...	91 (0.8 mm.)	C_8H_8ClNOS[i]	...	...	...	...	...	...
CH_3	CH_2	CO	218–219[a]	...	$C_{14}H_{11}ClN_4O_4S$[b,i]	45.8	45.5	3.0	2.8	15.3	15.2
CH_3	CH_2	CH_2	...	69–73 (17 mm.)	$C_8H_{10}S$	69.6	69.4	7.3	7.4	...	...
CH_3	CH_2	CHOH	51	114 (6 mm.)	$C_8H_{10}OS$	62.3	62.5	6.2	6.5	...	...

[a] Recrystallized from an ethanol-ethyl acetate mixtures. [b] 2,4-Dinitrophenylhydrazone. [c] Recrystallized from ethanol. [d] Oxime. [e] Calcd. for S, 18.6. Found: S, 18.9. [f] Semicarbazone. [g] Reference 2. [h] Calcd. for S, 15.0. Found: S, 15.1. [i] 2-Chloro derivative.

5-Chloro-2-(α-methylacrylo)thiophene.—The procedure described by Burckhalter and Sam (1) for the preparation of 2-(α-methylacrylo)thiophene was followed. From 145 Gm. (0.83 mole) of 5-chloro-2-propionylthiophene, 66.5 Gm. (0.83 mole) of dimethylamine hydrochloride, 24.9 Gm. (0.83 mole) of formaldehyde, there was obtained 49 Gm. (26%) of product, b.p. 130° (6 mm.); n_D^{28} 1.5576.

Anal.—Calcd. for C_8H_7ClOS: C, 51.5; H, 3.8. Found: C, 51.7; H, 4.0.

2-Chloro-5-methylthiaindan-6-one.—The procedure described by Burckhalter and Sam (1) for the preparation of 5-methylthiaindan-6-one was followed. From 48.7 Gm. (0.26 mole) of 5-chloro-2-(α-methylacrylo)thiophene there was obtained 20 Gm. (50%) of product, b.p. 91° (0.8 mm.); n_D^{25} 1.5887.

The 2,4-dinitrophenylhydrazone was prepared in the usual manner and recrystallized eight times from an ethanol–ethyl acetate mixture, m.p. 218–219°.

5-Methylthiaindan.—In a 500-ml. three-necked flask were placed 45.6 Gm. (0.3 mole) of 5-methylthiaindan-6-one, 30 ml. of 85% hydrazine hydrate, 40 Gm. (0.71 mole) of potassium hydroxide, and 300 ml. of diethylene glycol. The general method (7) for the Wolff-Kishner reaction was followed. The flask was heated on a steam bath until most of the potassium hydroxide had dissolved, then heated at reflux for 1 hour. The solution was partially distilled until the internal temperature of the flask reached 200°. The resulting solution was heated at 200° for 3 hours, cooled to 90°, and treated with 100 ml. of water. The reaction mixture was distilled until the internal temperature reached 200°. The oil from the aqueous distillate was separated, dried over calcium chloride, and distilled. Distillation was difficult because of foaming under reduced pressure. After distillation, 20 Gm. (50%) of product was obtained, b.p. 69–73° (17 mm.); n_D^{25} 1.5306. The infrared spectrum did not show carbonyl absorption between 1600 and 1700 cm.$^{-1}$

5-Methylthiaindan-6-ol.—In a 500-ml. three-necked flask fitted with a condenser, magnetic stirrer, and a dropping funnel a solution of 40 Gm. (0.265 mole) of 5-methylthiaindan-6-one in 200 ml. of methanol was placed. Through the dropping funnel 7.6 Gm. (0.2 mole) of sodium borohydride in 100 ml. of methanol was added with stirring. The addition of the sodium borohydride solution was regulated to keep the solution refluxing. After the addition of sodium borohydride, the reaction mixture was refluxed for 1 hour. The methanol was distilled *in vacuo;* the white solid was treated with 165 ml. of 20% sodium hydroxide solution and extracted three times with 100-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate. The ethereal solution was distilled to give 30 Gm. (75%) of product, b.p. 114° (6 mm.), m.p. 51–52°. The infrared spectrum in carbon tetrachloride showed characteristic hydroxyl absorption at 3550 cm.$^{-1}$, whereas carbonyl absorption was absent.

cis-2-Methyl-1-indanol.—The above procedure was followed using 12 Gm. (0.08 mole) of 2-methyl-1-indanone, 3.5 Gm. (0.1 mole) of sodium borohydride, and 200 ml. of methanol. Twelve grams (100%) of *cis*-2-methyl-1-indanol was obtained, m.p. 43–46° (lit. (12) m.p. 50–51°).

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