

barrier containing an interacting colloid material. Now  $D_m$  is given by (4)

$$D_m = \frac{P_m}{K_m}$$

where  $P_m$  and  $K_m$  are the permeability coefficient and partition coefficient for the compartment I phase and the colloid solution barrier phase. It has been shown (4) that  $P_m$  and  $P = D_1 K_1$  would be about the same for dilute colloid solutions, i.e., the steady state rates of the free solute contribution to transport and of the zero colloid case would be essentially the same. However,  $K_m$  would be greater than  $K_1$  by the factor

$$\frac{C_0 + MC_{b0}}{C_0}$$

Therefore,  $\tau$  in Eq. 14 would be greater than the  $\tau$  given by Eq. 1 by approximately this factor.

When  $D_e MC_{b0} \gg D_1 C_0$ , the lag time for the same problem will be determined by the transport rate of the colloid and we may write

$$\tau \sim \frac{h^2}{3D_e} \quad (\text{Eq. 15})$$

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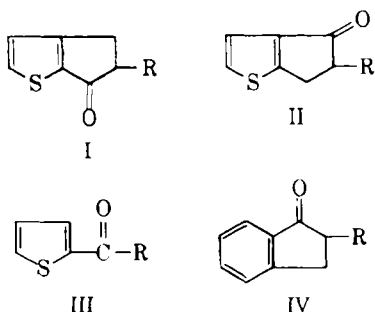
# Thiaindanones II

## Nitration, Acetylation, and Mannich Reactions

By JOSEPH SAM and ALONZO C. THOMPSON

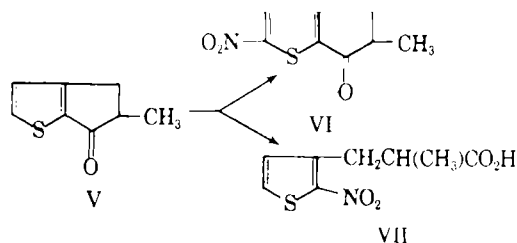
The nitration, acetylation, and Mannich reactions with thiaindanones are described. These reactions were observed to be analogous to similar reactions with 2-acylthiophenes and 1-indanone.

THIAINDANONES, represented by structures I and II, were observed to undergo reactions similar to those encountered with acylthiophenes (III) and indanones (IV).



The nitration of 5-methylthiaindanone (V) resulted in both ring substitution (VI) and in ring cleavage (VII). The ratio of nuclear substitution to carbonyl displacement was dependent

upon the temperature at which the nitration was performed. At a temperature below  $-6^\circ$  ( $-6$  to  $-15^\circ$ ) only the nuclear substituted nitro derivative was isolated, whereas above  $0^\circ$  ( $0$  to  $10^\circ$ ) both carbonyl displacement and ring substitution occurred (Table I).



Structures VI and VII were assigned to the nitration products on the basis of analysis, neutralization equivalent in the case of VII, and analogy to the nitration products of 2-acetylthiophene.

Rinkes (1) had shown earlier that replacement of the carbonyl group by the nitro group takes

TABLE I.—NITRATION OF 0.1 MOLE OF 5-METHYLTHIAINDAN-6-ONE

Temp., °C.	Ratio of VI/VII, Gm.
-15	10:0
-6	12:0
0	5:2
10	5:3

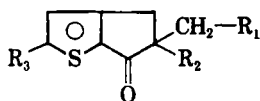
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TABLE II.—THIAINDAN-6-ONE MANNICH BASES

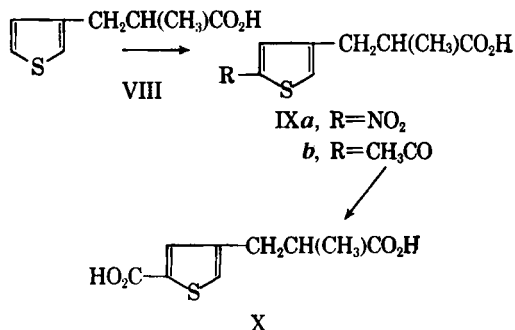


R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	M.p., °C.	Yield, %	Formula	Analyses, %					
						Calcd.			Found		
						C	H	N	C	H	N
(CH <sub>3</sub> ) <sub>2</sub> N	CH <sub>3</sub>	H	184–186 <sup>a</sup>	60	C <sub>11</sub> H <sub>10</sub> ClNOS <sup>b</sup>	53.81	6.52	5.70	53.69	6.56	5.67
C <sub>6</sub> H <sub>4</sub> NO <sup>c</sup>	CH <sub>3</sub>	H	184–186 <sup>a</sup>	30	C <sub>13</sub> H <sub>10</sub> ClNO <sub>2</sub> S <sup>b</sup>	54.26	6.26	...	54.29	6.26	...
C <sub>6</sub> H <sub>10</sub> N <sup>d</sup>	CH <sub>3</sub>	H	189–190 <sup>a</sup>	56	C <sub>14</sub> H <sub>10</sub> ClNOS <sup>b</sup>	58.84	7.00	...	59.01	7.08	...
(CH <sub>3</sub> ) <sub>2</sub> N	CH <sub>3</sub>	NO <sub>2</sub>	183–185 <sup>e</sup>	54	C <sub>11</sub> H <sub>10</sub> ClN <sub>2</sub> O <sub>4</sub> S <sup>b</sup>	45.43	5.16	9.63	45.67	5.13	9.16
(CH <sub>3</sub> ) <sub>2</sub> N	C <sub>6</sub> H <sub>5</sub>	H	103–104 <sup>a</sup>	57	C <sub>16</sub> H <sub>17</sub> NOS	70.85	6.24	5.17	70.60	6.45	5.03
(CH <sub>3</sub> ) <sub>2</sub> N	H	H	178–179 <sup>e</sup>	80	C <sub>10</sub> H <sub>10</sub> ClNOS <sup>b,f</sup>	51.83	6.04	6.04	52.01	5.88	6.08
(CH <sub>3</sub> ) <sub>2</sub> N	CH <sub>3</sub>	Cl	215 dec. <sup>g</sup>	72	C <sub>11</sub> H <sub>10</sub> Cl <sub>2</sub> NOS <sup>b</sup>	47.19	5.39	...	47.15	5.56	...
(CH <sub>3</sub> ) <sub>2</sub> N	CH <sub>3</sub>	H	186–188 <sup>g</sup>	72	C <sub>11</sub> H <sub>10</sub> ClNOS <sup>b,g</sup>	53.81	6.52	...	53.85	6.43	...

<sup>a</sup> Recrystallized from an ethanol-ethyl acetate mixture. <sup>b</sup> Hydrochloride. <sup>c</sup> Morpholino. <sup>d</sup> Piperidino. <sup>e</sup> Recrystallized from ethanol. <sup>f</sup> Calcd.: Cl, 15.33; S, 13.87. Found: Cl, 15.15; S, 13.85. <sup>g</sup> 5-Methyl-5-dimethylaminomethylthiaindan-4-one.

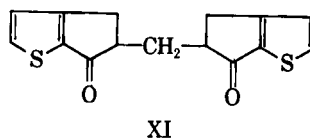
place during the nitration of 2-thiophenecarboxylic acid and 2-acylthiophenes at low temperature (–6°), but is secondary to nuclear substitution in the 5-position.

The nitration of  $\alpha$ -methyl- $\beta$ -(3-thienyl)propanoic acid (VIII) yielded a mononitro product different than VII. The yield was low (25%); most of the starting material was recovered. None of the 2-substituted derivative (VII), however, was isolated. The acylation of VIII also gave a mono acetylated product. The latter was oxidized with sodium hypobromite to yield a diacid. On the basis of earlier work by Hartough and Kosak (2) on the acylation of 3-methylthiophene and the work of Rinke (3) on the nitration of 3-methylthiophene, we have assigned structures IXa and IXb, respectively, to the products of the nitration and acylation of  $\alpha$ -methyl- $\beta$ -(3-thienyl)propanoic acid. Consequently, the diacid was assigned structure X.

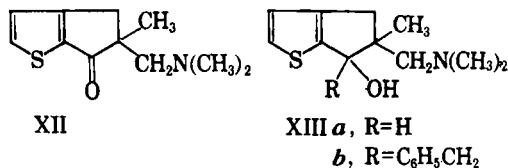


The applicability of the Mannich reaction to the thiaindanones was ascertained by the preparation of several Mannich bases (Table II). The reactions in ethanol, with one exception, proceeded smoothly and resulted in good yields of the expected products. This procedure, however, with the unsubstituted thiaindan-6-one (I, R = H),

resulted in the bis product (XI). The normal Mannich product was obtained when a mixture of benzene and nitrobenzene was used as a solvent.



The reduction of the Mannich ketone (XII) with sodium borohydride provided XIIIa, whereas the reaction of XII with benzyl magnesium bromide yielded XIIIb. Thus far, the esterification of XIIIa and XIIIb by the procedures described by Pohland and Sullivan (4, 5) and the procedure described by Burckhalter and Johnson (6) on related aminoalkanois has been unsuccessful.



Preliminary studies indicated that the Mannich bases (Table II), in general, exhibit antibacterial activity. A detailed report will be published at a later date.

#### EXPERIMENTAL<sup>1</sup>

**5-Methyl-2-nitro-thiaindan-6-one.**—*Method A.*—The procedure employed was essentially that described by Steinkopf and Jaffe (7) for the nitration of 2-acetylthiophene. A cold acetyl nitrate solution (prepared by the careful addition of 40 Gm. of

<sup>1</sup> 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.

fuming nitric acid, sp. gr. 1.50 to 50 ml. of acetic anhydride cooled to  $-6^{\circ}$ ) was added slowly with vigorous stirring to a solution of 20 Gm. (0.13 mole) of 5-methylthiaindan-6-one in 75 ml. of acetic anhydride maintained at  $10^{\circ}$ . After the addition was complete, the reaction mixture was stirred for 30 minutes and then poured, with stirring, into 200 ml. of cold water. The resulting oily layer was extracted 10 times with 40-ml. portions of ether; the combined extracts were washed three times with 100-ml. portions of 10% sodium bicarbonate solution. The ether solution was evaporated to dryness, and the resulting solid was recrystallized from ethanol to give 5 Gm. (21%) of product, m.p.  $98-100^{\circ}$ . The infrared spectrum in carbon tetrachloride showed sharp carbonyl absorption at  $1740\text{ cm.}^{-1}$ , nitro absorption at  $1340\text{ cm.}^{-1}$ , and the absence of nitro absorption at  $1520\text{ cm.}^{-1}$ .

*Anal.*—Calcd. for  $\text{C}_8\text{H}_7\text{NO}_2\text{S}$ : C, 48.76; H, 3.55; N, 7.17. Found: C, 49.06; H, 3.76; N, 7.37.

*Method B.*—The above procedure was followed, except that the reaction temperature was maintained at  $-6^{\circ}$ . From 15.2 Gm. (0.1 mole) of 5-methylthiaindan-6-one, there was obtained 11.7 Gm. (66%) of product, m.p.  $98-100^{\circ}$ . A mixed melting point with the product obtained by *Method A* showed no depression.

**$\alpha$ -Methyl- $\beta$ -(2-nitro-3-thienyl)propanoic Acid.**—The sodium carbonate wash solutions obtained in *Method A* were neutralized with 10% sulfuric acid and extracted five times with 100-ml. portions of ether. The ether was evaporated and the residual solid recrystallized from water to give 1 Gm. (4.5%) of product, m.p.  $135-136^{\circ}$ . The infrared spectrum in carbon tetrachloride showed carbonyl absorption at  $1690\text{ cm.}^{-1}$ , broad hydroxyl absorption beginning at  $3400\text{ cm.}^{-1}$  and extending to  $3000\text{ cm.}^{-1}$ , and sharp nitro absorption at  $1520\text{ cm.}^{-1}$ .

*Anal.*—Calcd. for  $\text{C}_8\text{H}_7\text{NO}_4\text{S}$ : C, 44.44; H, 4.18; neut. equiv., 215. Found: C, 44.38; H, 4.17; neut. equiv., 217.

The sodium carbonate solution from *Method B* did not yield acid materials.

**$\alpha$ -Methyl- $\beta$ -(5-nitro-3-thienyl)propanoic Acid.**—The procedure followed was that employed by Rinkes (3) for the nitration of 3-methylthiophene. A mixture of 15 Gm. (0.09 mole) of  $\alpha$ -methyl- $\beta$ -(3-thienyl)propanoic acid in 30 Gm. of acetic anhydride was added dropwise to an acetyl nitrate solution (prepared by the addition of 15 Gm. of nitric acid, sp. gr. 1.5, to 25 Gm. of acetic anhydride at  $0^{\circ}$ ). The resulting solution was stirred for an additional 20 minutes at a temperature maintained between  $0^{\circ}$  and  $-10^{\circ}$ , then poured with stirring into ice water and extracted 15 times with 50-ml. portions of ether. The ether was evaporated and the residual solid recrystallized from water to give 5.0 Gm. (25%) of product, m.p.  $95-96^{\circ}$ . The infrared spectrum in carbon tetrachloride showed sharp hydroxyl absorption at  $3500\text{ cm.}^{-1}$ , broad bonded hydroxyl absorption from  $3300$  to  $3000\text{ cm.}^{-1}$ , carbonyl absorption at  $1750\text{ cm.}^{-1}$ , and nitro absorption at  $1380\text{ cm.}^{-1}$ .

*Anal.*—Calcd. for  $\text{C}_8\text{H}_7\text{NO}_4\text{S}$ : C, 44.44; H, 4.18. Found: C, 44.68; H, 4.14.

**$\alpha$ -Methyl- $\beta$ -(5-acetyl-3-thienyl)propanoic Acid.**—A solution of 34 Gm. (0.2 mole) of  $\alpha$ -methyl- $\beta$ -(3-thienyl)propanoic acid and 20.4 Gm. (0.2 mole) of

acetic anhydride was stirred and heated to  $60^{\circ}$ . The source of heat was removed and 2 ml. of 85% orthophosphoric acid was added dropwise so that the temperature remained below  $90^{\circ}$ . Thereafter, the mixture was heated to  $100^{\circ}$  for 2 hours, then cooled to  $50^{\circ}$ , treated with 40 ml. of water and stirred rapidly for 30 minutes. The oil that separated was washed five times with water, taken up in 150 ml. of 10% sodium carbonate solution, reprecipitated with concentrated hydrochloric acid, and extracted with two 100-ml. portions of ether. The ether was evaporated and the residual oil distilled to give 16 Gm., b.p.  $140-160^{\circ}/0.5-2\text{ mm.}$  and 15 Gm. (35.4%), b.p.  $160-180^{\circ}/2\text{ mm.}$  Redistillation of the higher boiling fraction gave product, b.p.  $182^{\circ}/2.5\text{ mm.}$ ;  $n_D^{25}$  1.5548.

*Anal.*—Calcd. for  $\text{C}_{10}\text{H}_{11}\text{O}_3\text{S}$ : C, 56.60; H, 5.66; neut. equiv., 214. Found: C, 56.34; H, 5.83; neut. equiv., 213.

**$\alpha$ -Methyl- $\beta$ -(5-carboxy-3-thienyl)propanoic Acid.**—The procedure employed was adapted from that described by Farrar and Levine (8) for the oxidation of ketones to acids. A sodium hypochlorite solution (prepared by passing 32.2 Gm. (0.45 mole) of chlorine into a solution of 44 Gm. (1.1 moles) of sodium hydroxide in 60 ml. of water) was heated on a steam bath to  $55^{\circ}$  and treated dropwise with 10 Gm. (0.07 mole) of crude  $\alpha$ -methyl- $\beta$ -(5-acetyl-3-thienyl)propanoic acid so that the temperature did not rise above  $70^{\circ}$ . Thereafter, the mixture was heated to  $70^{\circ}$  and maintained at this temperature for 15 minutes. The excess sodium hypochlorite was decomposed by the addition of a solution of 50 Gm. of sodium bisulfite in 40 ml. of water. The solution was made acid to litmus with concentrated hydrochloric acid and extracted twice with 200-ml. portions of ether. The ether was evaporated and the resulting solid recrystallized seven times from water to give 5 Gm. (33%) of white crystals, m.p.  $158-160^{\circ}$ . The infrared spectrum in carbon tetrachloride showed maxima at  $1690\text{ cm.}^{-1}$  and at  $1710\text{ cm.}^{-1}$ , characteristic of aromatic and aliphatic carboxyl groups.

*Anal.*—Calcd. for  $\text{C}_9\text{H}_9\text{O}_4\text{S}$ : C, 50.47; H, 4.67; neut. equiv., 107. Found: C, 50.52; H, 4.92; neut. equiv., 107.

**Thiaindanone Mannich Bases (Table II).**—A mixture of 0.1 mole of the requisite thiaindanone, 0.1 mole of the amine hydrochloride, 0.1 mole of paraformaldehyde, 10 ml. of ethanol, and 1 ml. of concentrated hydrochloric acid was refluxed for 3 hours. The reaction mixture either was concentrated and treated with ether or poured, with stirring, into 100 ml. of acetone. The solid was removed by filtration and recrystallized from a suitable solvent.

**Bis-(6-oxo-5-thiaindanyl)methane.**—A solution of 10 Gm. (0.07 mole) of thiaindan-6-one, 3.0 Gm. (0.1 mole) of paraformaldehyde, 8.15 Gm. of dimethylamine hydrochloride, and 2 drops of concentrated hydrochloric acid in 30 ml. of ethanol was refluxed for 2 hours. The solid which precipitated from the solution was removed by filtration and washed with 10% sodium hydroxide solution and 5% hydrochloric acid. The solid was insoluble in the following hot solvents: ether, ethanol, water, benzene, toluene, dimethyl formamide, acetone, and dioxane. The material (15 Gm., 75%) was refluxed in toluene for 1 hour, filtered, and dried; m.p.  $156-158^{\circ}$ .

*Anal.*—Calcd. for  $C_{16}H_{12}O_2S_2$ : C, 62.47; H, 4.19. Found: C, 62.22; H, 4.37.

#### 5-Methyl-5-dimethylaminomethylthiaindan-6-ol.

—A modification of the procedure outlined by Chaikin and Brown (9) for the reduction of aldehydes and ketones was employed. To a solution of 18.9 Gm. (0.5 mole) of sodium borohydride in 400 ml. of 50% methanol, cooled to 20°, was added dropwise, with stirring, a solution of 5-methyl-5-dimethylaminomethylthiaindan-6-one (prepared from 56 Gm. (0.23 mole) of the hydrochloride) in 100 ml. of ethanol. The rate of addition of the ketone was controlled in order to maintain a reaction temperature of about 30°. The mixture, following the addition of the ketone, was heated for 2 hours at 50°. Thereafter, the mixture was concentrated *in vacuo* to a solid, treated with 200 ml. of water, and extracted with three 150-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate, separated from the drying agent by filtration, and concentrated *in vacuo*. The residual solid (23 Gm., 47.5%) was recrystallized from ethanol, to give product, m.p. 110–111°. The infrared spectrum of the product in carbon tetrachloride showed absorption at 3600  $cm^{-1}$  characteristic of hydroxyl groups, and the absence of the carbonyl absorption at 1660  $cm^{-1}$ .

*Anal.*—Calcd. for  $C_{11}H_{17}NOS$ : C, 62.56; H, 7.49; S, 5.17. Found: C, 62.39; H, 7.75; S, 15.00.

**5-Methyl-5-dimethylaminomethyl-6-benzylthiaindan-6-ol.**—The method of Gilman and Catlin (10) was used in the preparation of benzylmagnesium chloride. In a 1-L. three-necked flask fitted with a stirrer, dropping funnel, and a condenser provided with a drying tube containing calcium chloride and soda lime, were placed 9.5 Gm. (0.4 Gm. At.) of magnesium turnings, 25 ml. of dry ether, 5 ml. of a solution of 49.34 Gm. (0.3 mole) of benzyl chloride in 200 ml. of dry ether, and a crystal of iodine. Stirring was begun, and the remaining ethereal solution of benzyl chloride was added over

a period of 30 minutes and then refluxed for an additional 30 minutes.

The method of Pohland and Sullivan (5) was used for the Grignard reaction. To the Grignard reagent, prepared as described above, was added a solution of 16.1 Gm. (0.08 mole) of 5-methyl-5-dimethylaminomethylthiaindan-6-one in 200 ml. of dry ether over a period of 30 minutes. The reaction mixture was decomposed by the dropwise addition of a saturated solution of ammonium chloride. The ether was decanted from the solid and dried over anhydrous magnesium sulfate.

The ether solution was evaporated on a steam bath to give a red oil which partially crystallized on cooling in a dry ice-acetone bath. The solid substance (10 Gm., 44%) was removed by filtration and after several recrystallizations from ethanol melted at 113–115°. The infrared spectrum showed hydroxyl absorption at 3600  $cm^{-1}$  and the absence of the characteristic carbonyl maximum between 1600 and 1700  $cm^{-1}$ .

*Anal.*—Calcd. for  $C_{19}H_{23}NOS$ : C, 71.76; H, 7.64. Found: C, 71.81; H, 7.71. A white methiodide salt was prepared by the usual procedure and recrystallized from ethanol, m.p. 228° dec., darkening at 220°.

*Anal.*—Calcd. for  $C_{19}H_{23}INOS$ : C, 51.46; H, 5.85. Found: C, 51.63; H, 5.95.

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## Benzoxazoles: Potent Skeletal Muscle Relaxants

By JOSEPH SAM\* and JAMES N. PLAMPIN

The synthesis of a number of substituted 2-aminobenzoxazoles and benzoxazolinones is described. The majority of the compounds exhibit marked muscle relaxant activity, two of the most potent being 2-amino-5-chlorobenzoxazole<sup>1</sup> and 5-chlorobenzoxazolinone.<sup>2</sup>

AS EARLY AS 1943 Goodman and associates (1) reported that benzimidazole produced a reversible flaccid paralysis in various species of

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<sup>1</sup> Zoxazolamine. Marketed as Flexin by McNeil Laboratories.

<sup>2</sup> Chlorzoxazone. Marketed as Paraflex by McNeil Laboratories.

laboratory animals. However, it was not until 1952 when Domino and co-workers (2) investigated a series of benzoxazoles that more than a passing interest was expressed in this class of compounds.

The interesting pharmacological properties of the benzoxazoles mentioned above and the marked central nervous system depressant activity of substituted benzoxazolinones (3, 4) prompted