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Nonsteroidal Antiinflammatory Agents. III.[1] Syntheses of Benzothienothiepin, Benzothienoxepin and Their Acetic Acid Derivatives[2]

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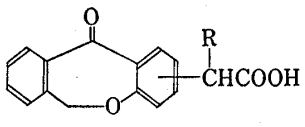
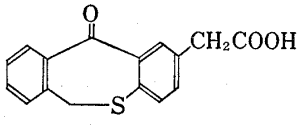
In order to search for new antiinflammatory agents, several acetic acid derivatives of sulfur containing tricyclic compounds were prepared. Initially, 4,10-dihydro-10-oxobenzo[*b*]thieno[2,3-*e*]thiepin (**3**) and 4,10-dihydro-4-oxobenzo[*b*]thieno[3,2-*e*]thiepin (**19**) were prepared by cyclization of 3-(phenylthiomethyl)thiophene-2-carboxylic acid (**2**) and 2-(phenylthiomethyl)thiophene-3-carboxylic acid (**18**), respectively, with polyphosphoric acid (PPA). The oxepin (**5**) corresponding to **3** was prepared by cyclization of the acid chloride of 3-(phenoxymethyl)thiophene-2-carboxylic acid (**4**) with aluminum chloride. However, cyclization of 2-(phenoxymethyl)thiophene-3-carboxylic acid (**20**) did not give the oxepin (**21**) corresponding to **19** but the rearranged compound, 4,10-dihydro-4-oxobenzo[*b*]thieno[2,3-*e*]oxepin (**22**). A similar rearrangement took place in the reaction of **4** with PPA yielding 4,10-dihydro-10-oxobenzo[*b*]thieno[3,2-*e*]oxepin (**7**). Furthermore, the acetic acid derivatives of **3**, **5** and **19** were prepared by methods similar to those used for the syntheses of unsubstituted tricyclic rings. These acetic acid derivatives exhibited good antiinflammatory activities, details of which will be reported elsewhere.

Keywords——benzothienothiepin; benzothienoxepin; acetic acid derivatives; cyclization; Friedel-Crafts reaction; rearrangement; mercaptophenyl acetic acid; antiinflammatory

In a previous paper,[4] we have reported the syntheses of 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepinacetic acids (A), many of which exhibited high antiinflammatory activities. 6,11-Dihydro-11-oxodibenz[*b*,*e*]thiepin-2-acetic acid (B) has been mentioned in Japanese Patent as



A R=H, Me



B

Fig. 1

possessing a similar activity.[5] This paper deals with the syntheses of the acetic acid derivatives of 4,10-dihydro-10-oxobenzo[*b*]thieno[2,3-*e*]thiepin (**3**) and oxepin analog (**5**) (see Chart 1) and 4,10-dihydro-4-oxobenzo[*b*]thieno[3,2-*e*]thiepin (**19**) and oxepin analog (**21**) (see Chart 2). Since these compounds are comparable to A or B in which one of benzene rings has been replaced by thiophene, their antiinflammatory activities are of interest in view of the structure-activity relationship.

1) Part II: T. Yoshioka, M. Kitagawa, M. Oki, S. Kubo, H. Tagawa, K. Ueno, W. Tsukada, M. Tsubokawa, and A. Kasahara, *J. Med. Chem.*, accepted.
2) This work was presented at the 96th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1976.
3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
4) K. Ueno, S. Kubo, H. Tagawa, T. Yoshioka, W. Tsukada, M. Tsubokawa, H. Kojima, and A. Kasahara, *J. Med. Chem.*, **19**, 941 (1976).
5) Yoshitomi Ltd., Jap. Patent 7200425 (1972).

The preparation of the tricyclic ring compound (**19**) by cyclization of the acid halide of S-(2-thenyl)thiosalicylic acid (**23**) with $ZnCl_2$ has been reported[6] (see Chart 2). This synthetic procedure could not be easily used for acetic acid derivatives desired for the present investigation, since the syntheses of the corresponding intermediates are troublesome. No syntheses of **3**, **5** and **21** have been reported to date.[7] Therefore, initial experiments were directed toward the preparation of these ring systems.

4,10-Dihydro-10-oxobenzo[*b*]thieno[2,3-*e*]thiepin (3) and -oxepin (5)

The intermediates, 3-(phenylthiomethyl)- and 3-(phenoxymethyl)thiophene-2-carboxylic acid (**2** and **4**) were readily prepared by treatment of ethyl 3-(bromomethyl)thiophene-2-carboxylate (**1**)[8] with thiophenol and phenol, respectively, followed by alkaline hydrolysis.

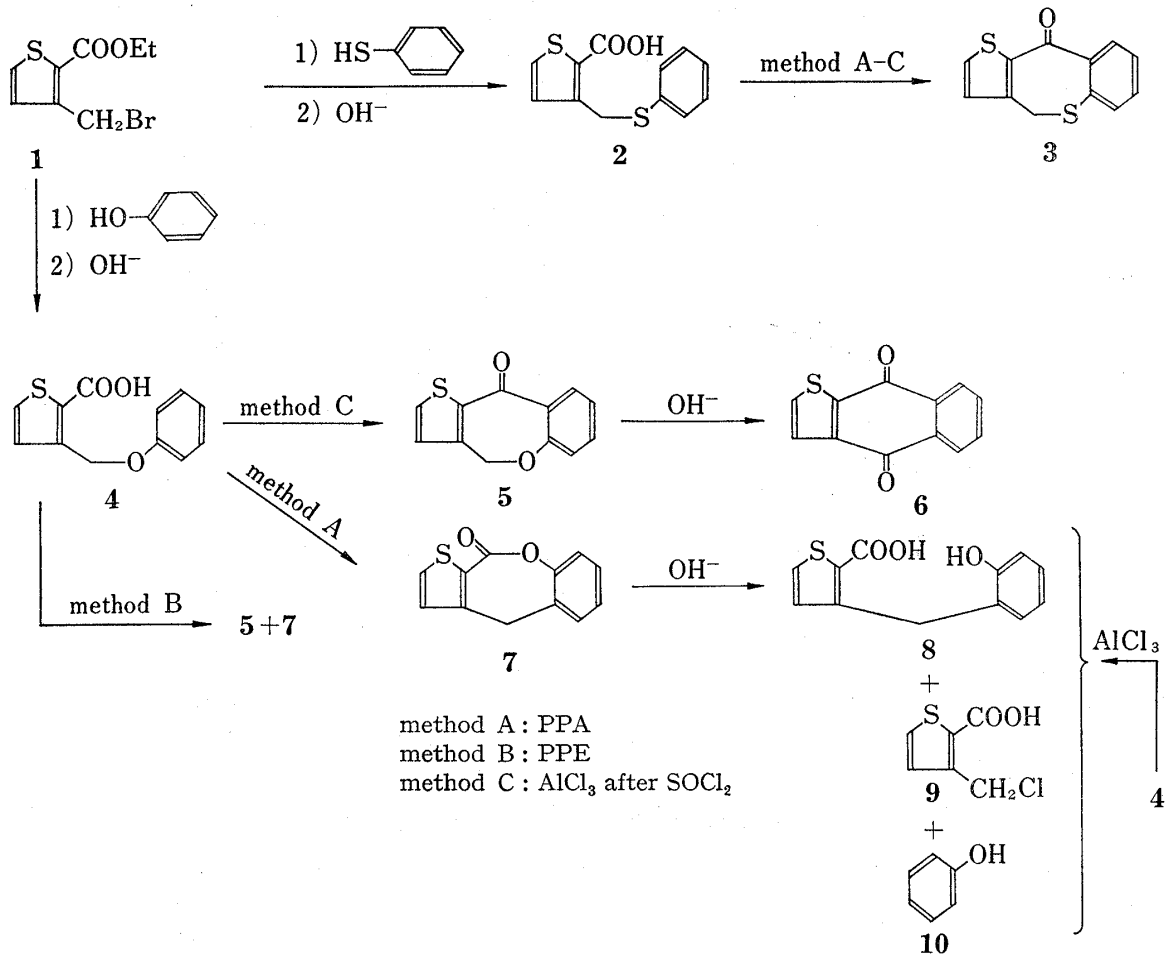


Chart 1

The carboxylic acid (**2**) thus produced was heated with polyphosphoric acid (PPA) at 95—100° giving the desired compound (**3**) in satisfactory yield (method A). Other methods of the cyclization of **2** using polyphosphate ester (PPE) at 115—120° (method B) and method C mentioned below gave **3** both in 34% yields. On the other hand, **4** was converted to the acid chloride with thionyl chloride and subsequent cyclization with aluminum chloride at room temperature provided **5** in 68% yield (method C). Cyclization of **4** with PPA at 60—

6) Sandoz Ltd., Neth. Appl. 6414154 (1965) [*C.A.*, **63**, 18091*b* (1965)].
7) After this work had been completed, the compound (**3**) was reported to prepared by the cyclization of 2-(3-thenylthio)benzoic acid with PPA-xylene: P. Caginiant and G. Kirsch, *C.R. Acad. Sci., Ser. C.*, **283**, 751 (1976).
8) V.N. Gogte, B.D. Tilak, K.N. Gadekar, and M.B. Sahasrabudhe, *Tetrahedron*, **23**, 2443 (1967).

70° gave, however, 4,10-dihydro-10-oxobenzo[*b*]thieno[3,2-*e*]oxepin (**7**) in 16% yield together with the unchanged **4** (32%), and **5** could not be obtained although the reaction was tried under various conditions. Cyclization of **4** with PPE at 120° gave a mixture of **5** and **7** (about 11:5; estimated by nuclear magnetic resonance (NMR) spectrum) in 25% yield together with the unchanged **4** (18%).

The structure of **7** was confirmed on the basis of the following spectral data and elemental analysis. The infrared (IR) spectrum showed an absorption at 1704 cm^{-1} due to C=O of ester. The NMR spectrum ($CDCl_3$) exhibited the signals at δ 4.03 due to methylene protons and δ 7.10—7.40 (4H, multiplet) due to benzene protons, of which signal pattern was similar to that of *o*-cresol. The mass spectrum gave the molecular ion peak at *m/e* 216. Further, alkaline hydrolysis of **7** gave 3-(2-hydroxybenzyl)thiophene-2-carboxylic acid (**8**), of which the IR spectrum showed the hydroxy band at 3380 cm^{-1} and the carbonyl band at 1640 cm^{-1}. The compound (**7**) probably resulted by alkyl aryl ether rearrangement and esterification. A similar reaction occurred when **4** was treated with aluminum chloride at room temperature, giving **8** (30% yield) together with 3-(chloromethyl)thiophene-2-carboxylic acid (**9**; 24% yield) and phenol (**10**; 5% yield). In the cases of the syntheses of 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin derivatives, no rearranged compound similar to **7** has been reported to date and also we could not isolate such a compound. These results indicate a difference of reactivities between benzyl and thenyl radicals.

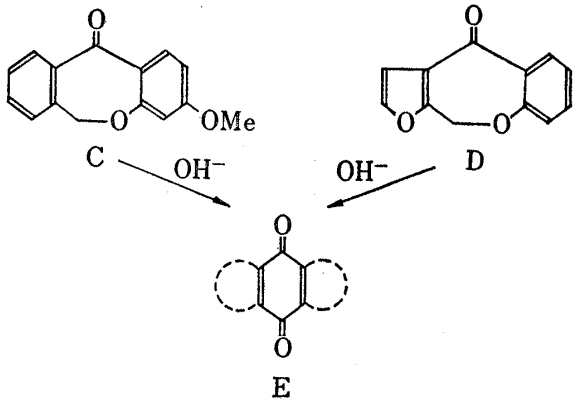


Fig. 2

Several oxepinones [for example, 3-methoxy-6,11-dihydrodibenz[*b*,*e*]oxepin-11-one (C) and 4,10-dihydrobenzo[*b*]furo[3,2-*e*]-oxepin-4-one (D)] were reported to be converted into quinones with base[9] (see Fig. 2). Davies *et al.*[9a] mentioned that this was caused by Wittig rearrangement of the corresponding carbanion followed by aerial oxidation of the product. New oxepinone (**5**) obtained in the present work was also converted into naphtho[2,3-*b*]thiophene-4,9-dione (**6**) in 91% yield by heating in 1 N potassium hydroxide solution at reflux temperature for 2hr.

4,10-Dihydro-4-oxobenz[*b*]thieno[3,2-*e*]thiepin (19) and -oxepin (21)

When a solution of 2-(hydroxymethyl)thiophene-3-carboxylic acid (**11**) in benzene was refluxed with *p*-toluenesulfonic acid, 2,5-dihydro-2-oxothieno[2,3-*c*]furan (**12**) was obtained only in 1% yield as Paulmier *et al.*[10] reported, and 2-benzylthiophene-3-carboxylic acid (**13**) was also obtained in 20% yield as the result of the Friedel-Crafts reaction. As the yield of **12** was very low, we abandoned an attempt to synthesize 2-(phenylthiomethyl)thiophene-3-carboxylic acid (**18**) or 2-(phenoxymethyl)thiophene-3-carboxylic acid (**20**) *via* **12** and proceeded the other route as shown in Chart 2. Esterification of **11** with a small amount of concentrated sulphuric acid in methanol gave methyl 2-(hydroxymethyl)thiophene-3-carboxylate (**14**) in 85% yield together with methyl 2-(methoxymethyl)thiophene-3-carboxylate (**15**) in 7% yield as the result of the reaction of thenyl radical with methanol. The reaction of **14** with thionyl chloride afforded methyl 2-(chloromethyl)thiophene-3-carboxylate (**16**) and a small amount of the dimer (**17**). Condensation of **16** thus obtained with thiophenol or phenol followed by alkaline hydrolysis afforded **18** or **20** in a good yield. The desired compound

9) *a*) J.S. Davies, V.H. Davies, and C.H. Hassall, *J. Chem. Soc.* (*C*), **1969**, 1873; *b*) C. Rivalle, E. Bisagni, and J. Andre-Louisfert, *Tetrahedron*, **30**, 3193 (1974).
10) C. Paulmier, J. Bourguigonon, J. Morel, and P. Pastour, *C.R. Acad. Sci., Ser. C.*, **270**, 497 (1970).

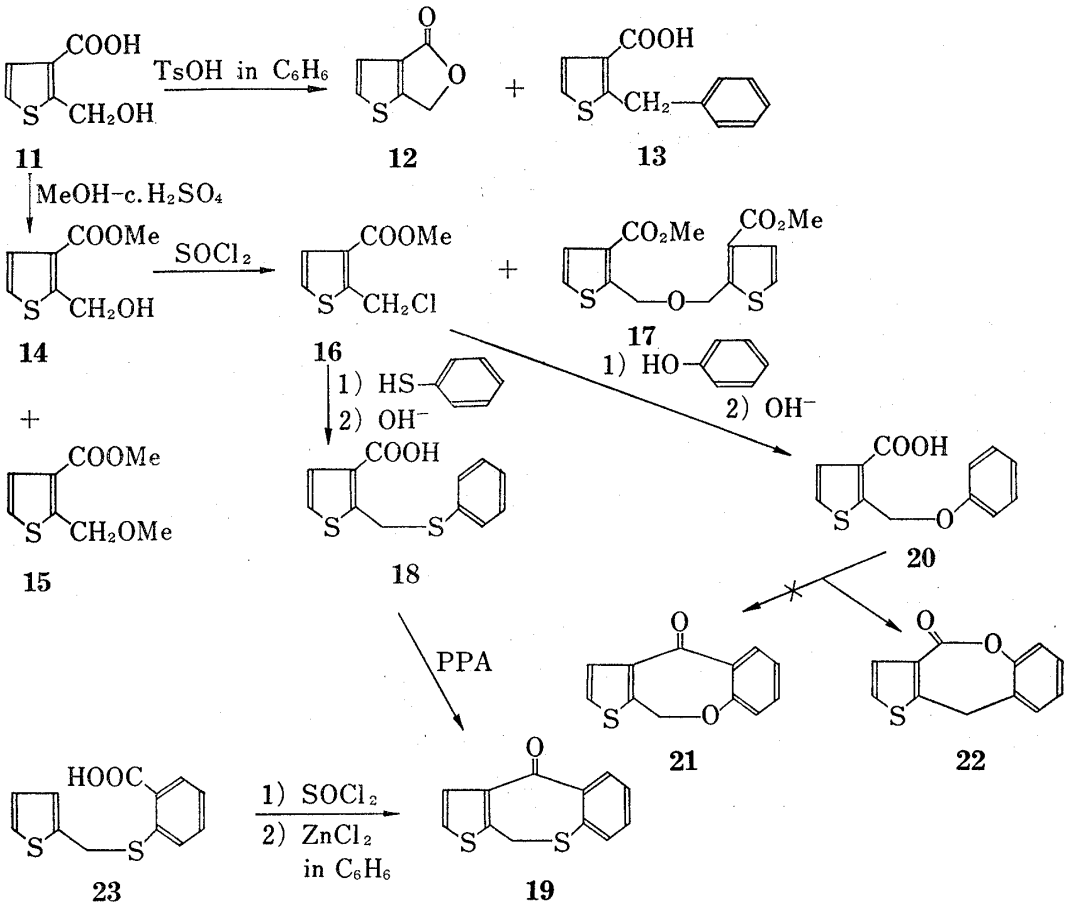


Chart 2

(**19**) was obtained by cyclization of **18** with PPA in a manner similar to that mentioned above. However, the cyclization of **20** using methods A–C gave no desired compound (**21**) but the rearranged compound, 4,10-dihydro-4-oxobenzo[*b*]thieno[2,3-*e*]oxepin (**22**) in 15—40% yield. All trials to obtain **21** by the methods A–C under various conditions (reaction temperature, time and cyclizing agents) were unsuccessful.

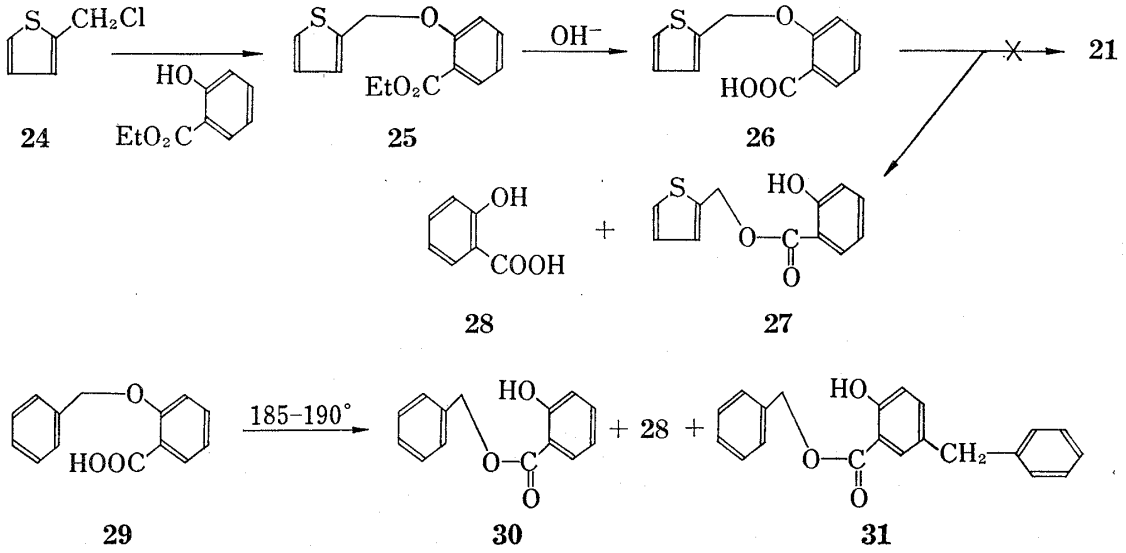


Chart 3

5 was obtained from **4**, whereas **21** could not be obtained from **20** by the method B and C. It is suggested that the negative charge at 3- and 2-position of thiophene relates to the chemical labilities of methylene-oxygen bonds of **4** and **20**.

Winthrop *et al.*[11] reported that the preparation of 6,11-dihydrodibenz[*b*,*e*]oxepin-11-one from 2-(benzyloxy)benzoic acid (**29**) with several cyclizing agents was unsuccessful. However, **19** was reported to be synthesized by cyclization of the acid halide of **23** with $ZnCl_2$, so we thought that the cyclization of 2-(2-thenyloxy)benzoic acid (**26**) might proceed. **26** was synthesized on reaction of 2-(chloromethyl)thiophene (**24**)[12] with ethyl salicylate followed by alkaline hydrolysis. It was so unstable that decomposed even at room temperature, and heating **26** at 80° for 30 min yielded salicylic acid (**28**) (25% yield) and 2-thenyl salicylate (**27**) (40% yield) in which the thenyl group had migrated from the ether-oxygen to the carboxyl group. Tarbell *et al.*[13] reported that the analogous reaction of **29** under drastic conditions gave **28** and rearranged products, **30** and **31**.

The reactions of thenyl derivatives were rarely known compared with those of the corresponding benzyl derivatives. The reactions mentioned above, *i.e.*, rearrangement reactions (**26**→**27**, **4**→**7**, and **20**→**22**) and condensation reactions (**11**→**13** or **15**), are new and of interest.

Syntheses of Acetic Acid Derivatives

Initially, mercaptophenylacetic acids (**39a—b**) required for the syntheses of acetic acid derivatives of **3** and **19** were prepared as shown in Chart 4. Thus, ethyl 3- or 4-hydroxyphenylacetate (**36a—b**) with diethylthiocarbamoylchloride[14] provided ethyl 3- or 4-(N,N-diethylaminothiocarbonyloxy)phenylacetate(**37a—b**) which were thermally rearranged to ethyl 3- or 4-(N,N-diethylaminocarbonylthio)phenylacetate (**38a—b**) according to Newman's procedure.[15] Alkaline hydrolysis of **38a—b** gave the desired **39a—b**.

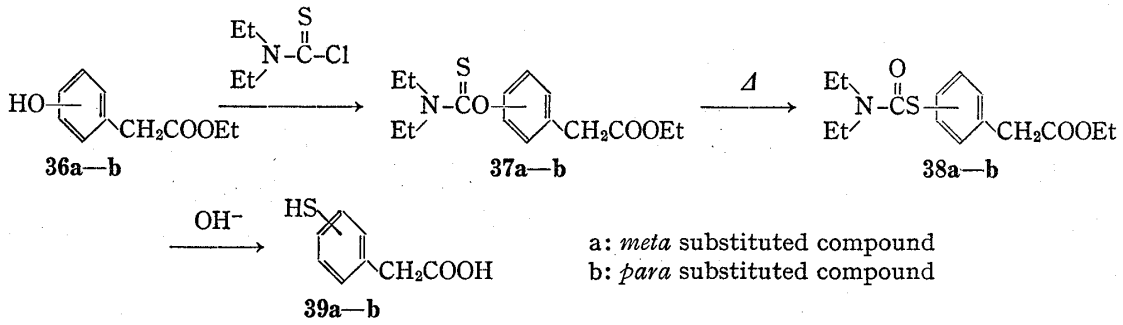


Chart 4

The condensation of **1** or **16** with **39** or hydroxyphenylacetic acids followed by alkaline hydrolysis gave various acid derivatives (**32a—e**, **33**), details of which were shown in Table I.

The cyclization of these intermediates in a manner similar to those used for the preparation of unsubstituted compounds yielded the desired acetic acid derivatives (**34a—e**, **35**),[16] details of which were shown in Table II.

11) S.O. Winthrop, M.A. Davis, F. Herr, J. Stewart, and R. Gaudry, *J. Med. Pharm, Chem.*, **5**, 1207 (1962).
12) K.B. Wiberg and H.F. McShane, "Organic Syntheses," Coll. Vol. III, ed. by E.C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 197.
13) D.S. Tarbell and V.P. Wystrach, *J. Am. Chem. Soc.*, **65**, 2146 (1943).
14) R.H. Goshorn, W.W. Levis, Jr., E. Jaul, and E.T. Ritter, "Organic Syntheses," Coll. Vol. IV, ed. by N. Rabjohn, John Wiley, and Sons, Inc., New York, 1963, p. 307.
15) M.S. Newman and H.A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966).
16) After this work had been completed, the compound (**34b**) was reported: D.E. Aultz and A.R. McFadden, *J. Med. Chem.*, **20**, 456 (1977).

Table I. Phenoxymethyl- and Phenylthiomethylthiophenecarboxylic Acids

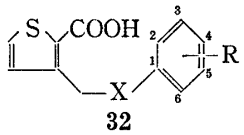
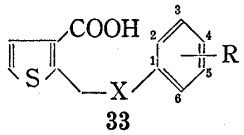
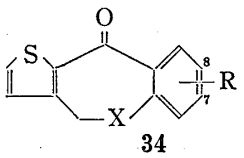
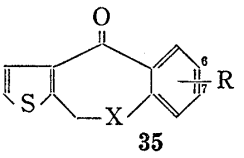
Compd. No.	X	R	mp (°C)	Recrystn solvent	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	S
		 **32**							
32a	O	3-CH_2COOH	187—189	AcOEt	58	$C_{14}H_{12}O_5S$	57.53 (57.64	4.14 4.24	10.97 10.66)
32b	O	4-CH_2COOH	229—232	EtOH-H_2O	56	$C_{14}H_{12}O_5S$	57.53 (57.66	4.14 4.31	10.97 10.64)
32c	O	3-$\overset{Me}{\overset{\vert}{C}}HCOOH$	192—194	AcOEt	57	$C_{15}H_{14}O_5S$	58.81 (58.53	4.61 4.62	10.47 10.35)
32d	S	3-CH_2COOH	171—173	AcOEt	71	$C_{14}H_{12}O_4S_2$	54.53 (54.58	3.92 3.97	20.80 20.51)
32e	S	4-CH_2COOH	187—189	AcOEt	66	$C_{14}H_{12}O_4S_2$	54.53 (54.52	3.92 4.11	20.80 20.62)
		 **33**							
33	S	3-CH_2COOH	146—148	AcOEt	67	$C_{14}H_{12}O_4S_2$	54.53 (54.73	3.92 4.03	20.80 20.62)

Table II. Thienobenzoxepin and -thiepin Analogs

Compd. No.	X	R	Method	mp (°C)	Recrystn solvent	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	S
		 **34**								
34a	O	7-CH_2COOH	C	139—141	AcOEt-C_6H_{14}	31	$C_{14}H_{10}O_4S$	61.30 (61.18	3.67 3.72	11.69 11.48)
34b	O	8-CH_2COOH	C	172—173	$CHCl_3$	40	$C_{14}H_{10}O_4S$	61.30 (61.48	3.67 3.78	11.69 11.93)
34c	O	7-$\overset{Me}{\overset{\vert}{C}}HCOOH$	C	142—143.5	C_6H_6	20	$C_{15}H_{12}O_4S$	62.49 (62.59	4.20 4.21	11.12 10.99)
34d	S	7-CH_2COOH	A	211—213	AcOEt	29	$C_{14}H_{10}O_3S_2$	57.91 (58.05	3.47 3.71	22.09 21.82)
34e	S	8-CH_2COOH	A	202—204	AcOEt	62	$C_{14}H_{10}O_3S_2$	57.91 (58.10	3.47 3.51	22.09 22.36)
		 **35**								
35	S	7-CH_2COOH	A	184—186	AcOEt	12	$C_{14}H_{10}O_3S_2$	57.91 (57.81	3.47 3.65	22.09 21.77)

The syntheses of thiepin derivatives were performed according to the method A used in the synthesis of **3**. On the other hand, the oxepin derivatives were synthesized according to the method C which was used in the preparation of **5** from **4** successfully.

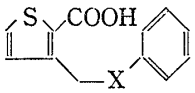
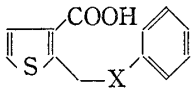
Benzothienothiepin- and benzothienoxepinacetic acid which were the products in this study, exhibited favorable antiinflammatory activities in the carrageenan-induced rat paw edema test, details of which will be reported elsewhere.[1)]

Experimental[17)]

3-(Phenylthiomethyl)thiophene-2-carboxylic Acid (2)——To a stirred solution of thiophenol (5.51 g, 0.05 mol) and Na (1.15 g, 0.05 g-atom) in EtOH (60 ml) was added a solution of **1** (12.4 g, 0.05 mol) in EtOH (50 ml) and the mixture was refluxed for 2 hr. After evaporation of the solvent, the residue was dissolved in H_2O and extracted with $CHCl_3$. Concentration of the extract gave a pale yellow oil. It was heated with KOH (11.2 g) in 60% EtOH (200 ml) at reflux temperature for 1 hr, concentrated to about 80 ml, cooled and acidified with HCl. The resulting precipitates were collected and crystallized from C_6H_6 to give **2** (8.74 g, 70%) as pale yellow needles, mp 142—143°. *Anal.* Calcd. for $C_{12}H_{10}O_2S_2$: C, 57.57; H, 4.03; S, 25.62. Found: C, 57.82; H, 3.99; S, 25.76.

The compounds (**4**, **18** and **20**) were prepared in a similar manner. Details were summarized in Table III.

Table III. Phenoxymethyl- and Phenylthiomethylthiophenecarboxylic Acids

Compd. No.	X	Starting material	mp (°C)	Recrystn solvent	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
									
4	O	1	148—151	C_6H_6	67	$C_{12}H_{10}O_3S$	61.52 (61.30	4.30 4.36	13.69 13.33)
									
18	S	16	135—136	C_6H_6	78	$C_{12}H_{10}O_2S_2$	57.57 (57.83	4.03 4.13	25.62 25.46)
20	O	16	163—165	C_6H_6	79	$C_{12}H_{10}O_3S$	61.52 (61.44	4.30 4.42	13.69 13.40)

Method A. 4,10-Dihydro-10-oxobenzo[*b*]thieno[2,3-*e*]thiepin (3)——A mixture of **2** (7.00 g, 28 mmol) and PPA (70 g) was stirred at 95—100° for 2.5 hr. The reaction mixture was carefully poured into ice water and extracted with $CHCl_3$. The extract was washed with 0.1 N NaOH, H_2O, dried (Na_2SO_4) and evaporated. The residue was crystallized from C_6H_6 to give **3** (4.86 g, 75%) as yellow needles, mp 133—135°. IR ν_{max}^{KBr} cm^{-1}: 1598 (C=O). NMR ($CDCl_3$) δ: 3.99 (2H, s, CH_2), 6.94 (1H, d, J=5 Hz, H_3), 7.55 (1H, d, J=5 Hz, H_2), 7.33—7.70 (3H, m, H_{6-8}), 8.05 (1H, m, H_9). *Anal.* Calcd. for $C_{12}H_8OS_2$: C, 62.04; H, 3.47; S, 27.60. Found: C, 62.01; H, 3.56; S, 27.31.

Reaction of **18** with PPA in a similar manner gave **19** in a yield of 46%. mp 114—115° (acetone). *Anal.* Calcd. for $C_{12}H_8OS_2$: C, 62.04; H, 3.47; S, 27.60. Found: C, 61.93; H, 3.51; S, 27.70.

17) The following instruments were used. IR spectra: a Hitachi 285 spectrophotometer; NMR (tetramethylsilane as the internal standard): a Hitachi R-20B spectrometer (60 MHz); Mass spectra (MS): a Hitachi Mass spectrometer RMS-4 (direct inlet, at 70 eV); Melting points: a Yanagimoto melting point apparatus. All melting points are uncorrected.

For column chromatography, silica gel (Merck, 70—230 mesh) was used. Thin-layer chromatography (TLC) was carried out on Merck Kieselgel GF_{254} plates and detected under ultraviolet light.

Polyphosphoric acid (PPA) was prepared from 85% H_3PO_4 (200 g) and P_2O_5 (290 g), and polyphosphate ester (PPE) was produced from EtOH (246 ml) and P_2O_5 (368 g), respectively.

Method B. 4,10-Dihydro-10-oxobenzo[*b*]thieno[2,3-*e*]thiepin (3)——A mixture of **2** (250 mg, 1 mmol) and PPE (2.5 g) was stirred at 115—120° for 20 min. The reaction mixture was treated in a manner similar to that described in method A to give **3** (80 mg, 34%).

Method C. 4,10-Dihydro-10-oxobenzo[*b*]thieno[2,3-*e*]oxepin (5)——A mixture of **4** (200 mg, 0.85 mmol) and $SOCl_2$ (1.3 ml) was refluxed for 1 hr and concentrated to dryness *in vacuo*. The residue was dissolved in nitrobenzene (3 ml), and $AlCl_3$ (200 mg) was added to the solution while stirring. After 1 hr, the reaction mixture was carefully poured into ice water and extracted with $CHCl_3$. The extract was washed with H_2O and dried. After evaporation of the solvent *in vacuo*, the product was isolated with column chromatography on silica gel [C_6H_6–$CHCl_3$ (1: 1)]. The resulting product was crystallized from ether–C_6H_{14} to give **5** (123 mg, 68%) as yellow needles, mp 78—79°. IR ν_{max}^{KBr} cm^{-1}: 1608 (C=O). NMR ($CDCl_3$) δ: 5.20 (2H, s, CH_2), 7.01 (1H, d, J=5 Hz, H_3), 7.10—7.60 (3H, m, H_{6-8}), 7.64 (1H, d, J=3 Hz, H_2), 8.20 (1H, m, H_9). *Anal.* Calcd. for $C_{12}H_8O_2S$: C, 66.65; H, 3.73; S, 14.83. Found: C, 66.52; H, 3.78; S, 14.67.

The compound (3) was also obtained from **2** in a similar manner (34% yield).

Reaction of 4 with PPA (Method A)——A mixture of **4** (1.00 g) and PPA (5.0 g) was heated at 60—70° for 1 hr, poured into ice water and extracted with $CHCl_3$. After evaporation of the solvent *in vacuo*, the residue was chromatographed on silica gel. The product eluted with C_6H_6 was crystallized from ether to give **7** (149 mg, 16%) as yellow crystals, mp 110—112°. IR ν_{max}^{KBr} cm^{-1}: 1704 (C=O). NMR ($CDCl_3$) δ: 4.03 (2H, s, CH_2), 7.00 (1H, d, J=5.5 Hz, H_3), 7.56 (1H, d, J=5.5 Hz, H_2), 7.10—7.40 (4H, m, H_{5-8}). MS *m/e*: 216 (M^+). *Anal.* Calcd. for $C_{12}H_8O_2S$: C, 66.65; H, 3.73; S, 14.83. Found: C, 66.67; H, 3.81; S, 14.75.

Elution with $CHCl_3$ and $CHCl_3$–MeOH gave **4** (317 mg).

Reaction of 4 with PPE (Method B)——A mixture of **4** (2.00 g) and PPE (20 g) was heated at 120° for 30 min, poured into ice water and extracted with $CHCl_3$. After evaporation of the solvent *in vacuo*, the residue was submitted to column chromatography on silica gel. The yellow crystals (470 mg, 25%) were obtained from the eluate with $CHCl_3$–benzene (10: 1), which were identified with a mixture of **5** and **7** (11: 5) by TLC (*Rf*s of **5** and **7** were 0.60, $CHCl_3$–MeOH=10: 1), NMR and IR.

Elution with $CHCl_3$–MeOH (10: 1) gave **4** (350 mg).

Naphtho[2,3-*b*]thiophene-4,9-dione (6)——A mixture of **5** (433 mg, 2.0 mmol) and KOH (1.18 g) in 60% EtOH (30 ml) was refluxed for 2 hr, concentrated to 10 ml and cooled. The resulting precipitates were collected and crystallized from acetone to give **6** (390 mg, 91%) as yellow needles, mp 229—230°. (Lit. 229—230°[18]). IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O). *Anal.* Calcd. for $C_{12}H_6O_2S$: C, 67.27; H, 2.83; S, 14.97. Found: C, 67.14; H, 2.88; S, 14.84.

3-(2-Hydroxybenzyl)thiophene-2-carboxylic Acid (8)——A mixture of **7** (433 mg, 2.0 mmol) and KOH (1.18 g) in 60% EtOH (30 ml) was refluxed for 2 hr, concentrated to 10 ml, cooled and acidified with HCl. The resulting precipitates were collected and recrystallized from AcOEt to give **8** (422 mg, 90%) as pale yellow crystals, mp 201—203°. IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 3000—2400 (COOH), 1640 (C=O). NMR (DMSO-d_6) δ: 4.27 (2H, s, CH_2). *Anal.* Calcd. for $C_{12}H_{10}O_3S$: C, 61.52; H, 4.30; S, 13.69. Found: C, 61.29; H, 4.31; S, 13.57.

The Reaction of 4 with $AlCl_3$——To a solution of **4** (2.34 g, 10 mmol) in $ClCH_2CH_2Cl$ (100 ml) was added $AlCl_3$ (2.67 g, 20 mmol) and stirred at room temperature for 40 min. The reaction mixture was poured into cold 1 N HCl (500 ml) and extracted with AcOEt. The organic layer was washed with H_2O, dried, concentrated to dryness and the residue was chromatographed on silica gel using $CHCl_3$–MeOH (20: 1). The phenol (**10**, 50 mg, 5%) was obtained from earlier eluate. Later eluate was crystallized from AcOEt to give **9** (362 mg, 21%) as colorless crystals, mp 163—165°. IR ν_{max}^{KBr} cm^{-1}: 1655 (C=O). NMR ($CDCl_3$) δ: 5.07 (2H, s, CH_2), 7.27 (1H, d, J=5 Hz, H_3), 7.82 (1H, d, J=5 Hz, H_2). *Anal.* Calcd. for $C_6H_5ClO_2S$: C, 40.80; H, 2.85; S, 18.15; Cl, 20.07. Found: C, 41.10; H, 3.02; S, 18.00; Cl, 19.92. Successive eluate was crystallized from AcOEt to give **8** (697 mg, 30%) as pale yellow crystals, identified with the authentic sample mentioned above.

Reaction of 11 with *p*-Toluenesulfonic Acid in Benzene——A mixture of **11** (1.75 g, 11 mmol) and TsOH·H_2O (1.14 g, 6.0 mmol) in C_6H_6 (130 ml) was refluxed for 6.5 hr, cooled, and H_2O was added. The insoluble material was filtered off. C_6H_6 layer was separated from the filtrate, concentrated *in vacuo* to dryness and the residue was chromatographed on silica gel using $CHCl_3$ and $CHCl_3$–MeOH (50: 1). Earlier eluate was crystallized from ether–C_6H_{14} to give **12** (15 mg, 1%), mp 130—132°. IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O). NMR ($CDCl_3$) δ: 5.35 (2H, s, CH_2), 7.25 (1H, d, J=5 Hz, H_4), 7.46 (1H, d, J=5 Hz, H_3). *Anal.* Calcd. for $C_6H_4O_2S$: C, 51.42; H, 2.88; S, 22.88. Found: C, 51.54; H, 3.18; S, 22.70. Later eluate was crystallized from ether–C_6H_{14} to give **13** (492 mg, 20%) as colorless needles, mp 123—125°. IR ν_{max}^{KBr} cm^{-1}: 1655 (C=O). NMR ($CDCl_3$) δ: 4.58 (2H, s, CH_2), 7.04 (1H, d, J=5.5 Hz, H_5), 7.48 (1H, J=5.5 Hz, H_4), 11.82 (1H, broad, COOH). *Anal.* Calcd. for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62; S, 14.69. Found: C, 65.74; H, 4.73; S, 14.85.

Methyl 2-(Hydroxymethyl)thiophene-3-carboxylate (14)——To a solution of **11** (4.46 g, 28 mmol) in MeOH (50 ml) was added conc. H_2SO_4 (1.6 ml) and the mixture was refluxed for 3.5 hr and worked up as usual.

18) V. Weinmayr, *J. Am. Chem. Soc.*, **74**, 4353 (1952).

The resulted product was crystallized from ether–C_6H_{14} to give **14** (4.11 g, 85%) as colorless needles, mp 61—62°. IR ν_{max}^{KBr} cm^{-1}: 1695 (C=O). NMR ($CDCl_3$) δ: 3.88 (3H, s, CH_3), 4.97 (2H, s, CH_2), 7.13 (1H, d, J=5.5 Hz, H_5), 7.43 (1H, d, J=5.5 Hz, H_4). *Anal.* Calcd. for $C_7H_8O_3S$: C, 48.82; H, 4.68; S, 18.62. Found: C, 48.84; H, 4.70; S, 18.42.

The mother liquor of crystallization was concentrated and the residue was distilled under reduced pressure to give **15** (353 mg, 7%) as a colorless oil, bp 66° (1 mmHg). IR ν_{max}^{neat} cm^{-1}: 1705 (C=O). NMR ($CDCl_3$) δ: 3.51 (3H, s, $-CH_2O\underline{CH_3}$), 3.84 (3H, s, $COOCH_3$), 4.98 (2H, s, CH_2), 7.16 (1H, d, J=5.5 Hz, H_5), 7.41 (1H, d, J=5.5 Hz, H_4). *Anal.* Calcd. for $C_8H_{10}O_3S$: C, 51.60; H, 5.41; S, 17.22. Found: C, 51.57; H, 5.13; S, 17.15.

Methyl 2-(Chloromethyl)thiophene-3-carboxylate (16)——A mixture of **14** (4.13 g, 24 mmol) and $SOCl_2$ was refluxed for 20 min and worked up as usual. The obtained product was distilled under reduced pressure to give **16** (3.80 g, 83%) as a colorless oil, bp 80—81° (1 mmHg). IR ν_{max}^{neat} cm^{-1}: 1706 (C=O). *Anal.* Calcd. for $C_7H_7ClO_2S$: C, 44.10; H, 3.70; Cl, 18.60; S, 16.82. Found: C, 43.89; H, 3.64; Cl, 18.77; S, 17.09.

The residue on distillation was recrystallized from C_6H_6 to give **17** (115 mg, 3%) as colorless needles, mp 111—112°. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). NMR ($CDCl_3$) δ: 3.84 (3H, s, CH_3), 5.21 (2H, s, CH_2), 7.18 (1H, d, J=5.5 Hz, H_5), 7.43 (1H, d, J=5.5 Hz, H_4). MS *m/e*: 326 (M^+). *Anal.* Calcd. for $C_{14}H_{14}O_5S_2$: C, 51.52; H, 4.32; S, 19.65. Found: C, 51.59; H, 4.21; S, 19.66.

4,10-Dihydro-4-oxobenzo[*b*]thieno[2,3-*e*]oxepin (22)——A mixture of **20** (200 mg, 0.85 mmol) and $SOCl_2$ was heated at reflux temperature for 1 hr and concentrated to dryness *in vacuo*. The oily residue was dissolved in $ClCH_2CH_2Cl$ (5 ml) and $AlCl_3$ (171 mg, 1.28 mmol) was added to the solution while stirring at 10—15°. After 30 min, the reaction mixture was poured into ice water, extracted with $CHCl_3$ and the washed, dried extract was concentrated. The residue was chromatographed on silica gel using C_6H_6 and the resulting product was crystallized from ether–C_6H_{14} to give **22** (64 mg, 38%) as yellow needles, mp 99—100°. IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O). NMR ($CDCl_3$) δ: 4.18 (2H, s, CH_2), 7.02 (1H, d, J=5.5 Hz, H_2), 7.45 (1H, d, J=5.5 Hz, H_3), 7.27 (4H, m, H_{6-9}). MS *m/e*: 216 (M^+). *Anal.* Calcd. for $C_{12}H_8O_2S$: C, 66.65; H, 3.73; S, 14.83. Found: C, 66.52; H, 3.74; S, 15.02.

The above reaction treated in nitrobenzene instead of $ClCH_2$–CH_2Cl also gave **22** in 35% yield. Furthermore, the reaction of **20** with PPE at 100—110° for 20 min or with PPA at 85—90° for 20 min gave **22** in a yield of 36% or 16%, respectively.

Ethyl *o*-(2-Thenyloxy)benzoate (25)——To a stirred solution of ethyl salicylate (3.32 g, 20 mmol) and Na (460 mg, 0.02 g-atom) in EtOH (30 ml) was added **24** (2.65 g, 20 mmol) and the mixture was stirred at room temperature for 2 hr. After evaporation of the solvent, the residue was dissolved in H_2O and extracted with $CHCl_3$. The extract was concentrated and chromatographed on silica gel using petr. ether–C_6H_6 (1:1) and C_6H_6. The isolated product was distilled to give **25** as a pale yellow oil, bp 80—90° (1 mmHg). IR ν_{max}^{neat} cm^{-1}: 1720, 1700 (C=O). NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7 Hz, CH_3), 4.35 (2H, q, J=7 Hz, $\underline{CH_2}CH_3$), 5.28 (2H, s, CH_2). *Anal.* Calcd. for $C_{14}H_{14}O_3S$: C, 64.10; H, 5.38; S, 12.22. Found: C, 64.35; H, 5.32; S, 12.12.

***o*-(2-Thenyloxy)benzoic Acid (26) and Its Migrated Compound (27)**——A mixture of **25** (307 mg, 1.2 mmol) and KOH (0.28 g) in 60% EtOH (5 ml) was refluxed for 1 hr and cooled. The reaction mixture was poured into ice water, acidified with HCl and extracted with ether. The extract was concentrated to dryness *in vacuo* at under 25° to give **26** (230 mg, 84%) as a pale yellow oil. IR ν_{max}^{neat} cm^{-1}: 1720 (C=O). NMR ($CDCl_3$) δ: 5.32 (2H, s, CH_2), 9.32 (1H, broad, COOH).

The compound (**26**, 305 mg, 1.3 mmol) was heated at 80° for 30 min and chromatographed on silica gel using petr. ether–C_6H_6 (1:1). The earlier eluate was crystallized from ether–C_6H_{14} to give **27** (123 mg, 40%) as colorless needles, mp 60.5—62°. (Lit. 58.7—61.2°[19]). IR ν_{max}^{KBr} cm^{-1}: 3120 (OH), 1665 (C=O). NMR ($CDCl_3$) δ: 5.50 (2H, s, CH_2). *Anal.* Calcd. for $C_{12}H_{10}O_3S$: C, 61.52; H, 4.30; S, 13.64. Found: C, 61.46; H, 4.34; S, 13.54.

The latter eluate was crystallized to give **28** (44 mg, 25%) as colorless needles, mp 157—159°, identified with the authentic sample.

Ethyl 3-(N,N-Diethylaminothiocarbonyloxy)phenylacetate (37a)——To a cooled solution of **36a** (27.0 g, 0.15 mol) in DMF (120 ml) was added, in small portions, 50% NaH (7.2 g). After hydrogen evolution ceased, the solution was cooled to 10° and diethylthiocarbamoyl chloride (29.7 g, 0.20 mol) was added all at once. The reaction mixture was heated at 40° for 1 hr. After cooling, the mixture was poured into H_2O and extracted with C_6H_6. The extract was washed with satd. NaCl solution, dried and concentrated to dryness. The brown oily residue (47.6 g) was chromatographed on silica gel. From the fraction eluted with C_6H_6, **37a** was obtained as a yellow oil (28.9 g, 65%). IR ν_{max}^{neat} cm^{-1}: 1727 (C=O), 1500 (C=S). The product was used to the next step without further purification.

Ethyl 3-(N,N-Diethylaminocarbonylthio)phenylacetate (38a)——Under a nitrogen atmosphere, **37a** (21.2 g, 0.72 mol) was heated over a temperature range of 235—240° for 2.5 hr, then cooled and chromatographed on silica gel. From the fraction eluted with C_6H_6–$CHCl_3$ (1:1), **38a** was obtained as a yellowish

19) L.P. Kyrides and F.B. Zienty, U.S. Patent 2519383 [*C.A.*, **45**, 663*c* (1951)].

brown oil (13.7 g, 65%). IR ν_{max}^{neat} cm^{-1}: 1732 (C=O), 1660 (C=O). The product was used to the next step without further purification.

3-Mercaptophenylacetic Acid (39a)——A mixture of **38a** (7.93 g, 28.8 mmol) and KOH (30 g) in 60% EtOH (200 ml) was refluxed under nitrogen atmosphere for 6.5 hr. The reaction mixture was worked up as usual and the obtained solid was crystallized from MeOH–H_2O to give **39a** as pale yellow crystals, mp 106—108°. IR ν_{max}^{KBr} cm^{-1}: 1693 (C=O). NMR ($CDCl_3$) δ: 3.40 (1H, s, SH), 3.52 (2H, s, CH_2), 9.67 (1H, broad, COOH). *Anal.* Calcd. for $C_8H_8O_2S$: C, 57.12; H, 4.79; S, 19.06. Found: C, 57.25; H, 4.84; S, 18.88.

From **36b**, 4-mercaptophenylacetic acid (**39b**) was obtained in a similar manner, mp 105° (lit. 105°[20]).

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20) J.I. Cunneen, C.G. Moore, and B.R. Shephard, *J. Appl. Polymer Sci.*, **3**, 11 (1960) [*C.A.*, **54**, 21822*c* (1960)].