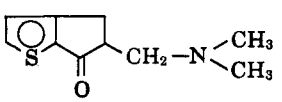
# Amino Derivatives of Thiophene Isosteres of Indanone and Tetralone

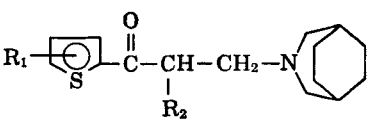
By J. SAM and G. G. ADVANI

**The investigation of α- and β-aminoketones derived from thiophene isosteres of 1-indanone and 1-tetralone is described. Preliminary pharmacological data are provided.**

IN THE COURSE of the investigation of thiophene isosteres of indanone it was observed (1) that 5-dimethylaminomethylthiaindan-6-one (I) possessed antimicrobial activity against both Gram-positive and Gram-negative organisms. This observation, along with the report (2) that Mannich bases (II) derived from 2-acylthiophenes possess antimicrobial activity against Gram-positive and Gram-negative organisms and that Mannich bases (III) derived from 1-tetralone possess tranquilizing properties (3), prompted the further investigation of amino derivatives of thiophene isosteres of both indanone and tetralone.



I



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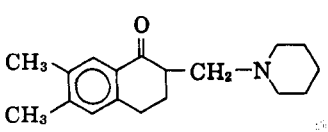

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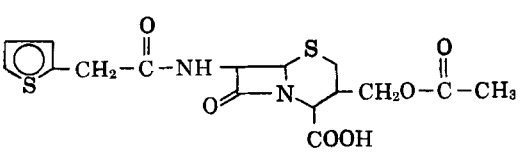
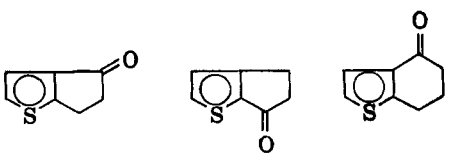


IV

The interesting antibacterial activity of the cephalosporin antibiotics (4) (cephalothin, IV) provided additional stimulus for continuing research with thiophene derivatives.

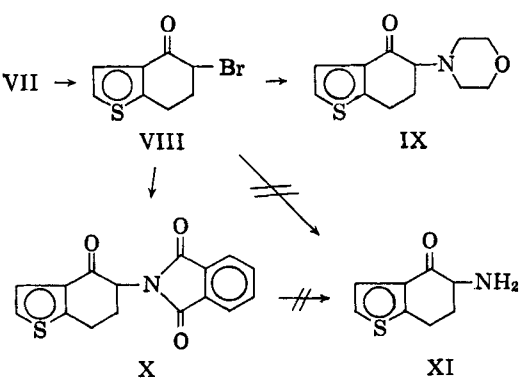
The intermediates thiaindan-4-one (V), thiaindan-6-one (VI), and 4-keto-4,5,6,7-tetrahydrothionaphthene (VII) were prepared according to procedures described in the literature. The aminoketones investigated are listed in Tables I and II.



V VI VII

## DISCUSSION

The preparation of the β-aminoketones was accomplished by well-known procedures (5) involving the Mannich reaction. The investigation of α-aminoketones was limited to derivatives of 4-keto-4,5,6,7-tetrahydrothionaphthene. The bromination of the latter compound provided a good yield (93%) of 5-bromo-4-keto-4,5,6,7-tetrahydrothionaphthene (VIII). The reaction of VIII with morpholine in a pressure bottle provided the corresponding α-amino-keto derivative (IX).



Scheme I

Preliminary attempts to prepare 5-amino-4-keto-4,5,6,7-tetrahydrothionaphthene (XI) have been unsuccessful. (See Scheme I.) The Delepine reaction (6) involving VIII did not yield the desired product. The reaction of VIII with potassium phthalimide provided the corresponding phthalimido derivative (X). The conversion of the latter compound to the corresponding α-amino derivative *via* alkaline hydrolysis or hydrazine hydrate, how-

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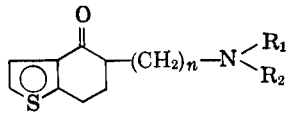
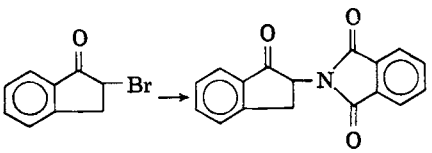
TABLE I.—AMINO-TETRAHYDROTHIONAPHTHENONES



| Compd. | $N(R_1)(R_2)$ | $n$ | M.p., °C. | % Yield | Molecular Formula | Anal., % Calcd. | Found |
|---|---|---|---|---|---|---|---|
| *1* | —$C_8H_4NO_2$[a] | 0 | 183–185 | 17 | $C_{16}H_{11}NO_3S$[b] | C, 64.5<br>H, 3.7<br>N, 4.7<br>S, 10.8 | C, 64.8<br>H, 3.8<br>N, 4.6<br>S, 10.7 |
| *2* | —$C_4H_8NO$[c] | 0 | 205–206 | 56 | $C_{12}H_{16}ClNO_2S$[b, d] | C, 52.6<br>H, 5.9<br>Cl, 13.3<br>N, 5.1<br>S, 11.7 | C, 52.8<br>H, 5.9<br>Cl, 13.0<br>N, 4.8<br>S, 11.7 |
| *3* | —$NHCH_3$ | 1 | 205–206 | 73 | $C_{10}H_{14}ClNOS$[b, d] | C, 51.8<br>H, 6.1<br>Cl, 15.3<br>N, 6.1<br>S, 13.8 | C, 52.0<br>H, 6.1<br>Cl, 15.2<br>N, 6.<br>S, 13.7 |
| *4* | —$N(CH_3)_2$ | 1 | 186–188 | 69 | $C_{11}H_{16}ClNOS$[b, | C, 53.7<br>H, 6.6<br>Cl, 14.4<br>N, 5.7<br>S, 13.0 | C, 53.7<br>H, 6.5<br>Cl, 14.4<br>N, 5.7<br>S, 12.9 |
| *5* | —$C_4H_8NO$[c] | 1 | 184–186 | 80 | $C_{13}H_{18}ClNO_2S$[b, d] | C, 54.2<br>H, 6.30<br>Cl, 12.3<br>N, 4.9<br>S, 11.1 | C, 54.1<br>H, 6.3<br>Cl, 12.3<br>N, 4.9<br>S, 11.0 |
| *6* | —$C_5H_{10}N$[e] | 1 | 180–182 | 53 | $C_{14}H_{20}ClNOS$[b, d] | C, 58.8<br>H, 7.1<br>N, 4.9<br>S, 11.2 | C, 58.8<br>H, 7.0<br>N, 5.1<br>S, 11.5 |
| *7* | —$NH—CH_2C_6H_5$ | 1 | 172–174 | 49 | $C_{16}H_{18}ClNOS$[b, d] | C, 62.4<br>H, 5.9<br>N, 4.6<br>S, 10.4 | C, 61.6<br>H, 5.8<br>N, 4.7<br>S, 10.5 |

[a] Phthalimido. [b] Recrystallized from absolute ethanol. [c] Morpholino. [d] Hydrochloride. [e] Piperidino.

ever, was unsuccessful. The corresponding 2-phthalimido-1-indanone (XII) was prepared as a model compound and also subjected to alkaline hydrolysis and hydrazine hydrate. However, preliminary attempts to obtain the corresponding 2-amino-1-indanone from the phthalimido derivative also were unsuccessful.



XII

**Pharmacological Results.**[1]—Most of the compounds described in this report were screened for CNS, cardiovascular, analgesic, anti-inflammatory, autonomic, antiallergic, and antispasmodic properties. None of the compounds exhibited pronounced activity in the tests performed. Compounds *3*, *4*, and *5* (Table I), when administered orally to rats, exhibited weak hypotensive effects at doses of 50 (300), 100(300), and 50(>300) mg./Kg., respectively. After oral administration to mice, compounds *2* and *5* (Table I) demonstrated weak analgesic activity at doses of 50(>300) and 150 (>300) mg./Kg., respectively, whereas compound *9* (Table II) possessed mild spinal cord depressant activity at 150(300) mg./Kg.

The numbers given in the parentheses above are oral doses at which toxicity was seen in mice.

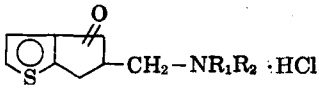
## EXPERIMENTAL[2]

**5-Bromo-4-keto-4,5,6,7-tetrahydrothionaphthene (VIII).**—The method used by Wilds (7) for the bromination of 1-keto-1,2,3,4-tetrahydrophenanthrene was modified and used for this preparation. To a solution of 5.66 Gm. (0.037 mole) of 4-keto-4,5,6,7-tetrahydrothionaphthene in 400 ml. of anhydrous ether kept at 0° was added dropwise with stirring 5.33 Gm. (0.033 mole) of bromine. Thereafter, the mixture was stirred at room temperature until the yellow insoluble addition complex which had formed dissolved completely. The ethereal solution was poured into ice water, separated from the aqueous layer, and washed with water and dilute sodium bicarbonate solution, respectively. Evap-

[1] The authors are grateful to Dr. M. H. Pindell, Bristol Laboratories, Syracuse, N. Y., for pharmacological data.

[2] All melting points were taken on a Fisher-Johns melting point apparatus and are corrected.

TABLE II.—SUBSTITUTED AMINOMETHYLTHIAINDANONES



| Compd. | $NR_1R_2$ | =O Position | M.p., °C. | % Yield | Molcular Formula | Anal., % Calcd. | Found |
|---|---|---|---|---|---|---|---|
| *8* | $-N(CH_3)_2$ | 4 | 169–170 | 65 | $C_{10}H_{14}ClNOS$[a] | C, 51.8<br>H, 6.1<br>Cl, 15.3<br>N, 6.1 | C, 52.0<br>H, 6.1<br>Cl, 15.2<br>N, 6.0 |
| *9* | $-NHCH_2C_6H_5$ | 4 | 199–201 | 85 | $C_{15}H_{16}ClNOS$[a] | C, 61.3<br>H, 5.5<br>N, 4.8 | C, 61.6<br>H, 5.5<br>N, 4.8 |
| *10* | $-C_5H_{10}N$[b] | 4 | 194–195 | 96 | $C_{13}H_{18}ClNOS$[a] | C, 57.7<br>H, 6.7<br>Cl, 13.0<br>N, 5.2 | C, 57.4<br>H, 6.9<br>Cl, 12.9<br>N, 5.1 |
| *11* | $-NHCH_3$ | 4 | 197–199 | 46 | $C_9H_{12}ClNOS$[a] | C, 49.7<br>H, 5.6<br>N, 6.4 | C, 50.5<br>H, 5.7<br>N, 5.9 |
| *12* | $-C_4H_8NO$[c] | 4 | 199–201 | 58 | $C_{12}H_{16}ClNO_2S$[a] | C, 52.6<br>H, 5.9<br>N, 5.1 | C, 52.8<br>H, 5.8<br>N, 5.0 |
| *13* | $-NH-CH_2C_6H_5$ | 6 | 188–190 | 68 | $C_{15}H_{16}ClNOS$[a] | C, 61.3<br>H, 5.5<br>N, 4.8 | C, 61.1<br>H, 5.6<br>N, 4.9 |
| *14* | $-C_4H_8NO$[c] | 6 | 175–177 | 88 | $C_{12}H_{16}ClNO_2S$[a] | C, 52.6<br>H, 5.9<br>N, 5.1 | C, 52.6<br>H, 5.9<br>N, 5.1 |
| *15* | $-NHCH_3$ | 6 | 190–192 | 70 | $C_9H_{12}ClNOS$ | C, 49.7<br>H, 5.6<br>N, 6.4 | C, 50.4<br>H, 5.7<br>N, 6.3 |

[a] Recrystallized from ethanol. [b] Piperidino. [c] Morphelino.

oration of the ether left 8.0 Gm. (93%) of product which was recrystallized from petroleum ether (b.p. range 30–60°), m.p. 79–81°.

*Anal.*—Calcd. for $C_8H_7BrOS$: C, 41.59; H, 3.05; Br, 34.57; S, 13.88. Found: C, 41.51; H, 3.15; Br, 34.37; S, 13.80.

**4-Keto-5-phthalimido-4,5,6,7-tetrahydrothionaphthene (X).**—The procedure devised by Sheehan and Bolhofer (8) for the preparation of phthalimidoacetophenone was used. Potassium phthalimide (1.98 Gm., 0.010 mole) was added in one portion to a stirred solution of 2.31 Gm. (0.1 mole) of 5-bromo-4-keto-4,5,6,7-tetrahydrothionaphthene in 20 ml. of *N,N*-dimethylformamide. After the mixture was stirred for 12 hr. at room temperature, 15 ml. of chloroform was added and the mixture poured into 50 ml. of water. The aqueous phase was separated and extracted with two 5-ml. portions of chloroform. The combined chloroform extract was washed with 10 ml. of 0.2 *N* sodium hydroxide and 10 ml. of water and thereafter dried over anhydrous sodium sulfate. After removal of the chloroform by distillation, the residual solid was triturated with 20 ml. of ether. The solid (0.5 Gm., 17%) was recrystallized several times from absolute ethanol, m.p. 183–185°.

*Anal.*—Calcd. for $C_{16}H_{11}NO_3S$: C, 64.45; H, 3.73; N, 4.71; S, 10.78. Found: C, 64.79; H, 3.82; N, 4.56; S, 10.66.

**4-Keto-5-morpholino-4,5,6,7-tetrahydrothionaphthene Hydrochloride (IX).**—The method used by Takahashi *et al.* (9) was employed. Two and three-tenths grams (0.01 mole) of 5-bromo-4-keto-4,5,6,7-tetrahydrothionaphthene, 1.64 Gm. (0.02 mole) of morpholine, and 30 ml. of anhydrous benzene contained in a pressure bottle were heated in an oil bath for 3 hr. at 100°. The precipitated morpholine hydrochloride was removed by filtration and the benzene distilled *in vacuo*. The residue was treated with 10% hydrochloric acid and extracted with ether. The aqueous layer was neutralized with excess sodium bicarbonate and extracted with ether. The ethereal solution was dried over sodium sulfate and thereafter treated with hydrogen chloride. The precipitate (1.5 Gm., 56%) was removed by filtration and recrystallized from absolute ethanol, m.p. 205–206°.

*Anal.*—Calcd. for $C_{12}H_{16}ClNO_2S$: C, 52.62; H, 5.89; Cl, 12.95; N, 5.12; S, 11.70. Found: C, 52.84; H, 5.88; Cl, 13.01; N, 4.81; S, 11.60.

**Mannich Bases (Tables I and II).**—*Method A.*—A mixture of 0.01 mole of ketone, 0.37 Gm. (0.0125 mole) of paraformaldehyde, 0.011 mole of appropriate amine hydrochloride, 10 ml. of absolute ethanol, and 1 drop of concentrated hydrochloric acid was refluxed on a steam bath for 4 hr. The alcohol was removed *in vacuo*, and the residual solid was washed several times with ether and recrystallized from absolute ethanol.

*Method B.*—The procedure utilized by Fry (10) for the Mannich reaction was followed. A mixture of 0.025 mole of appropriate amine hydrochloride, 0.75 Gm. (0.025 mole) of paraformaldehyde, 2 drops of concentrated hydrochloric acid, 4 ml. of nitrobenzene, and 4 ml. of benzene was refluxed in an oil bath for 20 min. This solution was treated with 0.025 mole of desired ketone and refluxed for an additional 30 min. During the last 12 min. of

reflux, the water was distilled from the reaction mixture. The residue was cooled, washed several times with ether, and recrystallized from absolute ethanol.

**2-Phthalimido-1-indanone (XII).**—The method of Curtin and Schmukler (11) was used. To 3.89 Gm. (0.021 mole) of potassium phthalimide in 15 ml. of *N,N*-dimethylformamide was added 6.34 Gm. (0.03 mole) of 2-bromo-1-indanone (crude). The mixture was heated on a steam bath with stirring for 8 hr. At the end of this period, the reaction mixture was poured into 120 ml. of water. The product (3.0 Gm., 36%) was removed by filtration and recrystallized several times from ethanol, m.p. 200–201°.

*Anal.*—Calcd. for $C_{17}H_{11}NO_3$: C, 73.62; H, 4.00; N, 5.05. Found: C, 73.79; H, 4.03; N, 5.07.

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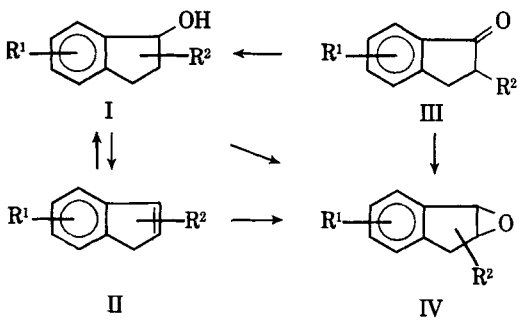
# Synthesis of 1,2-Epoxyindans

By JOSEPH SAM and T. C. SNAPP*

**Several substituted 1,2-epoxyindans have been prepared either by dehydrobromination of bromoindanols or by the peracid oxidation of indenes. It was observed that the course of ring opening of the epoxides with piperazine was dependent upon neighboring substituents. Preliminary screening of several of the compounds for antineoplastic activity has not revealed significant activity.**

ALTHOUGH EXTENSIVE investigations have been reported on cyclopentane- (1), cyclohexane- (2), and tetralin-1,2-epoxides (3), few reports (4–6) involving 1,2-epoxyindans (IV) have been published. The synthesis of substituted 1,2-epoxyindans was investigated through three methods: (*a*) dehydrobromination of 2-bromo-1-indanols (I, $R^2$ = 2-Br) by potassium hydroxide (7), (*b*) epoxidation of substituted indenes (II) with peracids (5), and (*c*) reduction of 2-bromo-1-indanones (III, $R^2$ = Br). (Scheme I.)

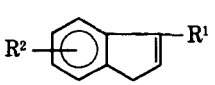



Scheme I

## DISCUSSION

The substituted indenes (II) utilized in this work were prepared by the dehydration of 1-indanols (I). The latter were derived from indanones (III) by the reduction with sodium borohydride or by the reaction with a Grignard reagent. Table I lists the novel indenes involved in this study.

TABLE I.—INDENES




| $R^1$ | $R^2$ |
|---|---|
| H | 6-$CH_3O$ (trimer)[a] |
| $C_6H_5$ | 7-Cl |
| H | 6-$CH_3O$-5-$C_6H_5CH_2O$ |
| $C_6H_5$ | 6-$C_6H_5CH_2O$ |
| $CH_3$ | 6-$CH_3O$ |

[a] The monomer has been described by Süs (8).

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