After drying ($Na_2SO_4$), the solvents were evaporated under reduced pressure. The gummy residue (5.14 g), which showed a strong OH ir band, was dissolved in 30 ml of anhydrous pyridine, the solution was chilled in ice, and 3.0 ml of $POCl_3$ was added cautiously. After standing for 20 hr at room temperature, the solution was poured on 250 g of crushed ice and the mixture was extracted ($Et_2O$). The extract was washed (dilute HCl, $H_2O$) and the ether was evaporated. The residue (4.45 g) gave from EtOH 2.09 g of **4**, mp 108–110°; the melting point did not change on recrystallization; nmr, 46.4 (t, 3, $CHCH_2CH_3$), 106.5 (m, 2, $CHCH_2CH_3$), 280.6 (t, 1, $CHCH_2CH_3$), 342.8 (s, 1, vinylic H), 345.7 cps (s, 1, vinylic H). *Anal.* ($C_{21}H_{18}$) C, H.

After treating the mother liquors of **4** with HCl, 0.78 g of 7-methyl-12-ethylbenz[*a*]anthracene (**5**),[12] mp 76–78°, could be isolated (lit.[12] mp 76–77°). Pure **4** was isomerized to its aromatic isomer **5** in quantitative yield by allowing its acetone solution to stand overnight with catalytic amounts of *p*-toluenesulfonic acid.

**7-Hydroxymethyl-12-ethylbenz[*a*]anthracene (5a).**—The solution of 6.40 g of **5** in 225 ml of glacial AcOH was stirred at 53° in an oil bath. Maintaining the temperature, a solution of 11.10 g (1.05 mole equiv) of $Pb(OAc)_4$ in 350 ml of AcOH was added over a period of 75 min. After stirring 30 min more, the warm solution was poured into 5 l. of ice water. The amorphous precipitate (7.78 g) was collected by filtration, dried, and chromatographed over 200 g of neutral alumina. Ether eluted 5.40 g of a partly crystalline material which was refluxed in 250 ml of a 1% methanolic KOH solution for 15 min. The warm solution was filtered from a small amount of resinous material, 2.5 ml of AcOH was added, and the solution was boiled down to about 40 ml. On cooling, 3.36 g of **5a**, mp 144–147°, crystallized. After two recrystallizations from MeOH, the compound melted at 146.5–148°; nmr, 103.0 (t, 3, $CH_2CH_3$), 115.9 (s, 1, OH), 225.6 (q, 2, $CH_2CH_3$), 325.3 cps (s, 2, $CH_2OH$). *Anal.* ($C_{21}H_{18}O$) C, H.

**7-Formyl-12-ethylbenz[*a*]anthracene (5b).**—One gram of **5a** was oxidized in 16 ml of anhydrous dioxane with 1.00 g (1.2 mole equiv) of DDQ for 17 hr at room temperature. The reaction mixture was worked up as for **2a**. The material obtained after filtration through alumina weighed 0.97 g and gave 0.84 g of **5b** when crystallized from hexane. The analytical sample melted at 92–94°; nmr, 100.9 (t, 3, $CH_2CH_3$), 230.1 (q, 2, $CH_2CH_3$), 680.2 cps (s, 1, CHO). *Anal.* ($C_{21}H_{16}O$) C, H.

**7-Ethyl-12-hydroxymethylbenz[*a*]anthracene (6a).**—To the stirred solution of 0.36 g of 7-ethyl-12-methylbenz[*a*]anthracene[10] in 14 ml of AcOH 0.62 g (1.05 mole equiv) of $Pb(OAc)_4$ in 20 ml of AcOH was added in the course of 80 min. A temperature of 58° was maintained throughout the addition and 30 min after. The warm solution was poured into 350 ml of ice water. The amorphous precipitate was filtered off, dried, and dissolved in ether. The solution was filtered through a column of 10 g of alumina. The residue from the evaporation of the filtrate was heated under reflux in 30 ml of a 1% methanolic KOH solution for 15 min. The solution was neutralized (AcOH) and the solvent was evaporated *in vacuo*. The oily residue (0.29 g) crystallized from a small amount of MeOH; yield 0.15 g of **6a**: mp 151–153°; nmr, 83.8 (t, 3, $CH_2CH_3$), 137.4 (s, 1, OH), 213.5 (q, 2, $CH_2CH_3$), 329.8 cps (s, 2, $CH_2OH$). *Anal.* ($C_{21}H_{18}O$) C, H.

**7-Isobutyl-12-methylbenz[*a*]anthracene (1g).**—12-Methylbenz[*a*]anthr-7-one[10] (5 g) was added to a stirred solution of *i*-BuMgBr prepared from 24 g of *i*-BuBr in 45 ml of $Et_2O$ and 85 ml of $C_6H_6$. The solution was stirred at room temperature for 19 hr and then heated under reflux for 1 hr. The reaction mixture was worked up as for **4**. The ir spectrum of the residue (5.80 g) obtained from the evaporated solvents showed an OH band. To dehydrate the intermediate carbinol, the material was dissolved in 100 ml of $C_6H_6$ and the solution was refluxed with 1.0 g of *p*-toluenesulfonic acid for 1 hr. The cooled solution was washed (dilute $Na_2CO_3$, $H_2O$). After drying, the solvent was removed. The residue (5.71 g) was chromatographed over 150 g of alumina. Petroleum ether eluted 2.78 g of a faintly yellow oil which crystallized from EtOH and gave 1.96 g of **1g**, mp 77–80°; after two recrystallizations from EtOH, mp 80–81°. *Anal.* ($C_{23}H_{22}$) C, H.

Crystalline material (1.5 g) was eluted with a mixture of petroleum ether (bp 30–60°)–ether (9:1). Recrystallization from hexane gave 1.18 g of pure 12-methylbenz[*a*]anthracene, mp 137–139° (lit.[10] mp 138–139°).

**7-Acetoxy-12-methylbenz[*a*]anthracene (1h).**—A solution of 6.0 g of 12-methylbenz[*a*]anthr-7-one[10] in 30 ml of AcOH and 30 ml of $Ac_2O$ was heated under reflux with 1.2 g of anhydrous $ZnCl_2$ for 2 hr. To the warm solution $H_2O$ was added cautiously until crystallization set in. After cooling, the crystals were collected, washed with MeOH, and dried: yield 5.97 g of **1h**, mp 193.5–195°. The melting point remained unchanged on recrystallization from EtOH. *Anal.* ($C_{21}H_{16}O_2$) C, H.

**7-Methoxy-12-methylbenz[*a*]anthracene (1i).**—To a solution of 12.60 g of *n*-BuMgBr in 45 ml of $Et_2O$ and 10 ml of $C_6H_6$ 6.00 g of **1h** was added with stirring. The resulting solution was refluxed for 1 hr. A solution of 22.00 g of $Me_2SO_4$ in 150 ml of toluene was then added. The mixture was warmed to 93–94° in an oil bath for 4 hr. $H_2O$ (100 ml) was added and the mixture was stirred at 90° for 1 hr more. After cooling, the organic layer was washed ($H_2O$) and dried ($Na_2SO_4$). Removal of the solvents left 5.94 g of an oil. This was dissolved in $C_6H_6$ and the solution was filtered through a column of 100 g of alumina. The column was washed with additional quantities of $C_6H_6$. The residue (5.02 g) obtained on evaporation of the solvent crystallized from hexane to give 3.16 g of **1i**, mp 75–77°. The twice recrystallized material melted at 76–77.5°. *Anal.* ($C_{22}H_{18}O$) C, H.

**7-Ethoxy-12-methylbenz[*a*]anthracene (1j)** was prepared from **1h** in exactly the same fashion as the 7-methoxy derivative, substituting $Et_2SO_4$ for $Me_2SO_4$. Six grams of **1h** yielded 2.49 g of the ethyl ether **1j**, mp 117–119°. For analysis, the material was recrystallized from hexane and melted at 118.5–119.5°. *Anal.* ($C_{23}H_{20}O$) C, H.

## Hypocholesterolemic Agents. Compounds Related to Ethyl α-(4-Chlorophenoxy)-α-methylpropionate

DONALD T. WITIAK,[1a] THOMAS CHUN-LUN HO, ROBERT E. HACKNEY,[1b]

*Divisions of Medicinal Chemistry, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210, and University of Iowa, Iowa City, Iowa 52240*

AND WILLIAM E. CONNOR

*Department of Internal Medicine, College of Medicine, University of Iowa, Iowa City, Iowa 52240*

*Received February 28, 1968*

In 1962 Thorp[2] reported that a combination of ethyl α-(4-chlorophenoxy)-α-methylpropionate (**1**)[3] and androsterone reduces serum lipid levels in experimental animals. Later, comparative studies on the mixture and **1** alone showed both to be equally effective in lowering elevated serum cholesterol levels and probably also in reducing elevated triglycerides.[4] Following these reports the hypocholesterolemic and hypolipidemic effects of **1** have been the subjects of numerous publications,[5,6] but the mechanism of action of the compound still re-

(1) (a) To whom reprint requests and inquiries concerning this work should be directed. (b) American Foundation for Pharmaceutical Education Fellow.

(2) J. M. Thorp, *Lancet*, **1**, 1323 (1962).

(3) Clofibrate, Chlorpenisate, ICI-28257, CPIB, Atromid-S, Regelan.

(4) M. F. Oliver, *J. Atherosclerosis Res.*, **3**, 427 (1963).

(5) (a) Symposium on Atromid, *ibid.*, **3**, 341 (1963); (b) M. M. Best and C. H. Duncan, *J. Lab. Clin. Med.*, **64**, 634 (1964); (c) D. S. Platt and J. M. Thorp, *Biochem. Pharmacol.*, **15**, 915 (1966).

(6) (a) J. Engstrom, *Acta Med. Scand.*, **180**, 519 (1966); (b) L. V. Baranova, *Kardiologiya*, **5**, 65 (1965); (c) V. Kallio and L. B. Soirander, *Gerontol. Clin.*, **8**, 349 (1966); (d) R. G. Gould, E. A. Swyryd, B. J. Coan, and D. R. Avoy, *J. Atherosclerosis Res.*, **6**, 555 (1966); (e) E. D. Hocking, R. Chakrabarti, J. Evans, and C. R. Fearnley, *ibid.*, **7**, 121 (1967); (f) V. S. Zadionchenko, *Sov. Med.*, **30**, 77 (1967); (g) E. S. Argain, M. D. Bogdonoff, and C. Cain, *Arch. Internal Med.*, **119**, 80 (1967); (h) R. W. Robinson and R. J. LeBeau, *Amer. J. Med. Sci.*, **253**, 106 (1967); (i) J. W. Davis, S. J. Wilson, and J. R. McField, *ibid.*, **252**, 697 (1966); (j) J. R. O'Brien and J. B. Heywood, *Thromb. Diath. Haemorrhag.*, **16**, 768 (1966); (k) A. Herrernan, N. J. Hickey, R. Mulcahy, and R. MacFarlane, *Irish J. Med. Sci.*, **490**, 423 (1966); (l) G. Frandoli, A. Gibelli, and P. Giarola, *Clin. Terap.*, **38**, 27 (1966); (m) E. Giety, *Med. Klin.* (Munich), **62**, 336 (1967).

mains obscure. Two theories receiving the most attention have been the thyroxine release mechanism[5,7] and inhibition of cholesterol biosynthesis.[8]

According to the thyroxine release mechanism **1** may undergo rapid *in vivo* hydrolysis to the free acid[2] which exerts its effect, at least in part, by displacement of thyroxine from its binding proteins in the plasma followed by redistribution of the hormone between the plasma and liver.[5] The result is presumed to be increased lipid metabolism[9] with concomitant lowering of serum lipid levels because of the hyperthyroid effect in the liver.[5c] Although studies[10] with euthyroid patients reveal that **1** produces no significant change in the glycine to taurine conjugate ratio with biliary bile acids as is the case with hypothyroid patients treated with thyroid hormones,[11] the authors[10] suggest that these observations are not conclusive negative evidence for the thyroxine release mechanism. Preliminary experiments indicated **1** resembles 2,4-dichlorophenoxyacetic acid which alters the physiological distribution of thyroxine but leaves the concentration of free thyroxine in the plasma and output of pituitary thyrotropin essentially unchanged, producing these effects principally by an action on the liver.[12]

Alternatively, the maximum effect of **1** on rat serum cholesterol corresponds to periods of maximum thyroid and adrenocortical function[9] and causes an increase in weight, protein concentration, and nonfasting glycogen levels of liver in the monkey, dog, and rat.[5c] Serum and tissue esterases rapidly hydrolyze **1** *in vitro* and *in vivo*[2,8a] and the resulting acid has been shown to depress thyroxine binding to (1) prealbumin in human plasma, (2) $\alpha$-globulin and albumin in dog plasma, and (3) albumin in rat plasma.[7] Thyroidectomy also abolishes the effect of **1** on serum cholesterol.[5b,c]

Studies in humans demonstrate that **1** produces no significant decrease in urinary 17-keto or 17-ketogenic steroids.[13] It has been suggested that since most of the patients in these studies were hypercholesterolemic, steroid production is not dependent upon a reduction of the serum cholesterol from elevated to normal levels.[14] However, when given to rats at 0.2% of the diet, **1** significantly decreases the secretion of adrenal steroids and *in vitro* inhibition of steroidogenesis is dose related to the reduction of adrenal steroids and the hypocholesterolemic effect.[14]

In the ethyl $\alpha$-phenoxy-$\alpha$-methylpropionate series mechanism of action has been investigated only with **1** which is reported to be the most active analog.[2,15] If, however, analogs were to be found having *in vivo* activity equal to **1**, subsequent parallel *in vitro* studies may serve to differentiate between possible mechanisms of action on a structural basis. This report relates our initial attempt to define structure–action relationships and to find other active compounds which may then be studied *in vitro*.

## Results

A series of ethyl $\alpha$-(4-substituted phenoxy)-$\alpha$-methylpropionates were prepared. Condensation of the appropriately *para*-substituted phenol with acetone and chloroform in the presence of sodium hydroxide followed by esterification of the resulting acid afforded the desired esters in 30–35% over-all yield.[16] In this series only the unsubstituted compound **4** exhibited significant hypocholesterolemic activity ($p < 0.05$) in normocholesterolemic rats. The activity of **4** compares reasonably well with that of **1** when the drug is administered orally, mixed with the diet (Table I). No significant hypocholesterolemic activity was observed at 0.15, 0.20, and 0.50% drug in the diet for the *p*-$CH_3O$ (**3**), $CH_3$ (**2**), and CN (**5**) analogs.

*p*-$RC_6H_4OC(CH_3)_2CO_2C_2H_5$

**1**, R = Cl
**2**, R = $CH_3$
**3**, R = $CH_3O$
**4**, R = H
**5**, R = CN

TABLE I
BIOLOGICAL ACTIVITY

| Compd | % drug in diet | Wt, g[a] | Wt, g, after 12 days[b] | Serum cholesterol, mg %[c] |
|---|---|---|---|---|
| Control (I) | ... | 536 | 522 | 104 ± 5[d] |
| 1 | 0.15 | 450 | 471 | 74 ± 4 |
| | 0.20 | 514 | 471 | 64 ± 4 |
| | 0.50 | 489 | 455 | 71 ± 5 |
| 4 | 0.15 | 415 | 432 | 84 ± 6 |
| | 0.20 | 460 | 481 | 81 ± 7 |
| | 0.50 | 460 | 481 | 60 ± 4 |
| Control (II) | ... | 585 | 591 | 104 ± 7 |
| DL-7 | 0.20 | 600 | 607 | 87 ± 9 |
| | 0.50 | 614 | 591 | 85 ± 6 |
| D-(+)-7 | 0.20 | 583 | 523 | 98 ± 8 |
| | 0.50 | 588 | 511 | 83 ± 7 |
| L-(−)-7 | 0.20 | 627 | 595 | 79 ± 7 |
| | 0.50 | 639 | 608 | 72 ± 8 |

[a] Average weight of six rats at the beginning of the experiment. [b] Average weight of six rats after 12 days on diet. [c] Average value for six rats. [d] Standard error of the average value.

Removal of one of the *gem*-dimethyl groups of **1** affords the desmethyl analog **6** which is readily synthesized by condensation of sodium *p*-chlorophenolate with ethyl $\alpha$-bromopropionate.[17] Hydrolysis of the resulting ethyl $\alpha$-(4-chlorophenoxy)propionate (**6**) followed by resolution of the resulting acid **7** with (−)-brucine af-

(7) Y.-H. Chang, R. Pinson, Jr., and M. H. Malone, *Biochem. Pharmacol.*, **16**, 2053 (1967).

(8) (a) J. M. Thorp and W. S. Waring, *Nature*, **194**, 948 (1962); (b) D. R. Avoy, E. A. Swyryd, and R. G. Gould, *J. Lipid Res.*, **6**, 369 (1965); (c) P. J. Nestel, E. Z. Hirsch, and E. A. Couzens, *J. Clin. Invest.*, **44**, 891 (1965); (d) D. L. Azarnoff, D. R. Tucker, and G. A. Barr, *Metab. Clin. Exptl.*, **14**, 959 (1965); (e) D. L. Azarnoff and D. R. Tucker, *Fed. Proc.*, **23**, 552 (1964); (f) S. W. Teal and W. Gamble, *Biochem. Pharmacol.*, **14**, 896 (1965).

(9) (a) J. M. Thorp, *J. Atherosclerosis Res.*, **3**, 351 (1963); (b) J. M. Thorp in "The Control of Lipid Metabolism," J. K. Grant, Ed., Biochemical Society Symposia, Oxford, Academic Press Inc., New York, N. Y., 1963, p 163.

(10) A. S. Truswell, W. D. Mitchell, and S. McVeigh, *J. Atherosclerosis Res.*, **6**, 591 (1966).

(11) (a) K. Hellstrom and J. Sjovall, *ibid.*, **1**, 205 (1961); (b) K. Hellstrom and S. Lindstedt, *J. Lab. Clin. Med.*, **63**, 666 (1964).

(12) C. Osorio, K. W. Walton, C. H. W. Browne, D. West, and P. Whystock, *Biochem. Pharmacol.*, **14**, 1479 (1965).

(13) C. Berry, A. Moxham, E. Smith, A. E. Kellie, and J. D. N. Nabarro, *J. Atherosclerosis Res.*, **3**, 380 (1963).

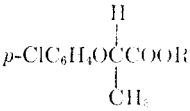
(14) D. H. Huffman and D. L. Azarnoff, *Steroids*, **9**, 41 (1967).

(15) (a) W. G. M. Jones, J. M. Thorp, and W. S. Waring, British Patent 860,303 (1961); (b) J. M. Thorp, British Patent 898,596 (1962).

(16) (a) M. Julia, M. Baillarge, and G. Tschernoff, *Bull. Soc. Chim. France*, 776 (1956); (b) G. Bargellini, *Gazz. Chim. Ital.*, **36**, 334 (1906); *Chem. Zentr.*, **2**, 326 (1906); C. A. Bishoff, *Ber.*, **33**, 933 (1900).

(17) A. A. Aroyan and V. V. Darbinyan *Izv. Akad. Nauk Arm. SSR, Khim. Nauk*, **16**, 59 (1963).

fords the (−) acid[18,19]; resolution with (+)-yohimbine yields the (+) enantiomorph.[20]



DL-**6**, R = $C_2H_5$
DL-**7**, R = H

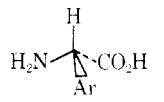
Analysis of the optical rotatory dispersion (ORD) and circular dichroism (CD) curves for both the (+) and (−) acids, liberated after three to five recrystallizations of their respective salts to constant rotation at the sodium D line, confirm the optical purity of the compounds and reveal their absolute configurations to be D-(*R*) and L-(*S*), respectively.[21] The ethyl esters prepared from the optically pure acids gave similar ORD and CD curves (see Experimental Section). Compounds of the D-(+) configuration exhibit a positive Cotton effect for the optically active aromatic chromophore with a peak at 288–290 mμ (positive shoulder at 283–284 mμ), a trough at 264–265 mμ, and a positive plain dispersion curve for the optically active carbonyl chromophore between 260 and 235 mμ. These data are in agreement with the work of Sjoberg[21] who observed a positive plain dispersion curve in the region between 700 and 300 mμ for a series of D-α-phenoxypropionic acids and amides. Instrumentation limitations did not allow Sjoberg to observe the remaining spectrum at shorter wavelengths than 300 mμ.

Ethyl L-(−)-α-(4-chlorophenoxy)propionate (**6**) exhibits significant hypocholesterolemic activity ($p < 0.05$) in normocholesterolemic rats. While the apparent hypocholesterolemic activity of the D and DL compounds is not significant, the activity of the L isomer compares favorably with the hypocholesterolemic effect of **1** at similar dosages.

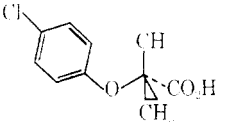
## Discussion

It thus far appears that the minimum structural requirements for analogs of compound **1** having activity are (a) no functional group in the *para* position of the phenyl ring, and (b) only one methyl group on the α carbon but in the correct configuration L-(−)-**7**. It may be possible to obtain a greater discrimination of activities with hypercholesterolemic rats or other animals. Using normocholesterolemic rats the compounds tested could only be classified as significantly active or inactive at the three dosage levels employed.

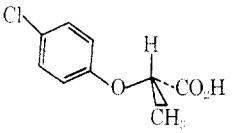
If one assumes that an aryl ether oxygen may interact with a protein in a manner not unlike an amino group, then L-(−)-α-(4-chlorophenoxy)propionic acid (**7**), the possible metabolic product of L-**6**, is biologically most closely related by configuration to L-thyroxine (**8**). If one further assumes that L-thyroxine is bound to protein by means of its $CO_2H$, $NH_2$, and Ar groups, one explanation for the greater activity of the L ester **6** might be that the L acid, formed after *in vivo* hydrolysis, more readily competes with L-thyroxine for an asymmetric binding site on a protein by means of the $CO_2H$, ether oxygen, and methyl groups. In the case of the D acid **7** the methyl group apparently has the wrong configuration; with the *gem*-dimethyl acid **1**, one of the methyl groups must have the right configuration.



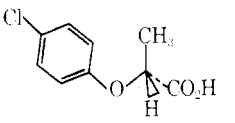
**8**, L-thyroxine
Ar = (3,5-diiodo-4-hydroxyphenoxy)-3,5-diiodophenyl



**1**, α-(4-chlorophenoxy)-α-methylpropionic acid



**7**, L-(−)-α-(4-chlorophenxoy)-propionic acid



**7**, D-(+)-α-(4-chlorophenoxy)-propionic acid

However, there are several alternative possibilities why the D and L esters show differing hypocholesterolemic activity: (1) the D acid is formed less readily from the ester *in vivo*, and/or (2) it is bound to a greater extent than the L or *gem*-dimethyl compound to protein sites of loss, and/or (3) the D acid is excreted more readily, and/or (4) the L acid acts mainly as a stereoselective inhibitor of cholesterol biosynthesis not related to L-thyroxine. We are currently attempting to determine which of these proposals or combinations of proposals represents a most likely explanation for the differences observed for drug activity *in vivo*.

Rats were weighed before and after the 12-day feeding period as a measure of drug toxicity. All rats consumed the entire diet. No relationship exists between the loss or gain of weight and the hypocholesterolemic effect (Table I). Control groups varied by about ±10 g. While the average weight loss for rats on a diet containing 0.20 and 0.50% L-(−)-**7** or **1** was about the same (30–35 g), rats on the D-(+)-**7** diet lost an average of 70 g. Rats feeding on 0.20 or 0.50% diets of the deschloro compound **4** gained an average of 20 g, indicating this compound may be less toxic than **1**.

### Experimental Section

**Chemical.**—Melting points are corrected and were taken using a Thomas–Hoover melting point apparatus. Optical rotary dispersion and circular dichroism measurements were recorded with a Durrum-Jasco spectropolarimeter. Rotations at the sodium D line were taken with a Zeiss polarimeter.

**Ethyl α-(4-substituted phenoxy)-α-methylpropionates** were prepared by the method of Bargelline[16b] described by Julia, *et al.*[16a] Both known and unknown compounds are described in Table II.

**Ethyl DL-α-(4-chlorophenoxy)propionate** (**6**) was synthesized in the usual manner by refluxing equimolar parts of sodium 4-chlorophenolate and ethyl α-bromopropionate in ethyl methyl ketone.[17] 4-Chlorophenol (94 g, 0.7 mole) and ethyl 2-bromopropionate (122.5 g, 0.7 mole) were refluxed for 48 hr with 276.4 g of $K_2CO_3$ in 500 ml of MeCOEt. The reaction mixture was cooled and poured into 500 ml of $H_2O$. The ketone layer was separated and the $H_2O$ layer was further extracted ($Et_2O$), dried ($Na_2SO_4$), and filtered, and the combined ether and ketone layers were concentrated under reduced pressure affording 150 g (89%) of **6**, bp 155–158° (20 mm), lit.[18] bp 130° (0.7 mm).

**DL-α-(4-Chlorophenoxy)propionic acid** (**7**) was prepared from 150 g of (0.65 mole) of **6** by refluxing in 10% aqueous NaOH with stirring for 2 hr affording 121.9 g (66%) of DL acid. Recrystal-

(18) (a) M. Julia and G. Tschernoff, *Bull. Soc. Chim. France*, 934 (1957); (b) L. Haskelberg, *J. Org. Chem.*, **12**, 426 (1947).
(19) (a) M. Matell, *Arkiv Kemi*, **7**, 437 (1954); (b) D. Osborne, R. L. Wain, and R. Walker, *J. Hort. Sci.*, **27**, 44 (1952).
(20) M. S. Smith, R. L. Wain, and F. Wightman, *Ann. Appl. Biol.*, **39**, 295 (1952).
(21) B. Sjoberg, *Arkiv Kemi*, **15**, 451 (1960).

TABLE II

| Compd | Formula | Analyses[a] | Bp, °C (mm) Obsd | Bp, °C (mm) Lit. |
|---|---|---|---|---|
| 1 | $C_{12}H_{15}O_3Cl$ | C, H | 160–164 (30) | 138 (10)[16a] |
| 2 | $C_{13}H_{18}O_3$ | C, H | 175–180 (30) | 139 (4)[16a] |
| 3 | $C_{13}H_{18}O_4$ | C, H | 150–154 (30) | 140–142 (8)[16a] |
| 4 | $C_{12}H_{16}O_3$ | C, H | 138–142 (30) | 160–165 (7)[16b] |
| 5 | $C_{13}H_{15}O_3N$ | C, H, N | 154–156 (4) | ... |

[a] Analyses were determined by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by Clark Microanalytical Laboratory, Urbana, Ill., and were within ±0.4% of the calculated values.

lization from petroleum ether (60–80°) afforded white crystals, mp 113–114°, lit.[19a] mp 114.5–115.5°.

L-(−)-α-(**4-Chlorophenoxy**)**propionic Acid** (**7**).—Finely powdered (−)-brucine (16.7 g, 0.042 mole) was suspended in 2 l. of boiling 20% EtOH in $H_2O$. To the stirred suspension was added 20 g (0.1 mole) of DL-**7** in 50 ml of 1 *N* NaOH and 50 ml of EtOH. The mixture was stirred with boiling until a clear solution resulted. The solution was filtered and on cooling the salt crystallized. Five additional recrystallizations from 20% EtOH–$H_2O$ afforded 10.6 g (44%) of brucine salt, $[\alpha]^{25}D$ −25.4° (*c* 1.9720, MeOH). Utilizing twelve times these amounts 122 g of optically pure salt was obtained. The acid was liberated from 122 g of salt by acidification with 5% $H_2SO_4$ and extraction with ether. The ether was dried ($Na_2SO_4$), filtered, and removed under reduced pressure affording after recrystallization from petroleum ether (60–80°), 28.8 g (70%) of L-(−)-**7**: mp 104–105°, lit.[19a] mp 103.5–104.5°; $[\alpha]^{25}D$ −34.95° (*c* 5.0078, MeOH), lit.[19a] $[\alpha]^{25}D$ −40.1° (EtOH); RD (*c* 0.0242, MeOH) (24–25°), $[\phi]_{325}$ −567°, $[\phi]_{310}$ −803°, $[\phi]_{300}$ −1320°, $[\phi]_{290}$ −2650°, $[\phi]_{283}$ −1800 (sh), $[\phi]_{277}$ 0°, $[\phi]_{267}$ +1130°, $[\phi]_{264}$ +1180, $[\phi]_{260}$ +990, $[\phi]_{250}$ 0°, $[\phi]_{245}$ −710°, $[\phi]_{240}$ −1460°; CD (*c* 0.2420, MeOH) (24–25°), $[\theta]_{300}$ 0°, $[\theta]_{289}$ −2620°, $[\theta]_{285}$ −1750°, $[\theta]_{282}$ −2990°, $[\theta]_{273}$ −2310°, $[\theta]_{254}$ −500°, $[\theta]_{240}$ −2500°.

D-(+)-α-(**4-Chlorophenoxy**)**propionic acid** (**7**) was obtained from DL-**7** by the method of Smith, *et al.*,[20] for resolving similar compounds. Resolution was accomplished utilizing (+)-yohimbine obtained from the HCl salt. Three recrystallizations of the yohimbine salt of D-(+)-**7** from $Me_2CO$ afforded white crystals, $[\alpha]^{25}$ +64.8° (*c* 2.3220, MeOH). The D-(+) acid was liberated from the salt as in L-(−)-**7** above. Recrystallization from petroleum ether (60–80°) afforded white crystals: mp 104–105°, lit.[19a] mp 103.5–104.7°; $[\alpha]^{25}D$ +34.1° (*c* 3.6720, MeOH), lit.[19a] $[\alpha]^{25}D$ +39.8 (EtOH); RD (*c* 0.0261, MeOH) (24–25°), $[\phi]_{325}$ +610°, $[\phi]_{310}$ +830°, $[\phi]_{300}$ +1180°, $[\phi]_{290}$ +2580°, $[\phi]_{283}$ +1700° (sh), $[\phi]_{277}$ 0°, $[\phi]_{269}$ −660°, $[\phi]_{264}$ −880°, $[\phi]_{250}$ 0°, $[\phi]_{24}$ +790°, $[\phi]_{240}$ +1490°; CD (*c* 0.2610, MeOH) (24–25°), $[\theta]_{300}$ 0°, $[\theta]_{288}$ +1850°, $[\theta]_{285}$ +2600°, $[\theta]_{270}$ +1560°, $[\theta]_{268}$ +1450°, $[\theta]_{253}$ +460°, $[\theta]_{240}$ +2020°.

**Ethyl** L-(−)-α-(**4-Chlorophenoxy**)**propionate** (**6**).—The L-(−) acid **7** (12 g, 0.06 mole) was refluxed with 100 ml of EtOH containing 4 ml of $H_2SO_4$ for 24 hr. The solution was poured into 200 ml of $H_2O$ and extracted ($Et_2O$). The ether was washed with 5% $NaHCO_3$, dried ($Na_2SO_4$), filtered, and removed under reduced pressure affording after distillation 8.8 g (65%) of L-(−)-**6** ester: bp 150–152° (20 mm); $[\alpha]^{25}D$ −46.2° (*c* 5.0120, MeOH), lit.[18a] $[\alpha]^{25}D$ −52.7° (EtOH); RD (*c* 0.0302, MeOH) (24–25°), $[\phi]_{325}$ −680°, $[\phi]_{305}$ −1020°, $[\phi]_{300}$ −1330°, $[\phi]_{289}$ −2460°, $[\phi]_{284}$ −1740° (sh), $[\phi]_{280}$ −830°, $[\phi]_{274}$ 0°, $[\phi]_{270}$ +680°, $[\phi]_{266}$ +720°, $[\phi]_{261}$ +640°, $[\phi]_{253}$ 0°, $[\phi]_{250}$ −530°, $[\phi]_{240}$ −1480°; CD (*c* 0.3020, MeOH) (24–25°), $[\theta]_{300}$ −300°, $[\theta]_{289}$ −2350°, $[\theta]_{286}$ −2050°, $[\theta]_{282}$ −2750, $[\theta]_{278}$ −2250°, $[\theta]_{275}$ −2450°, $[\theta]_{254}$ −900°, $[\theta]_{245}$ −1600°.

**Ethyl** D-(+)-α-(**4-Chlorophenoxy**)**propionate** (**6**) was prepared in similar yields and by the same method used for the L-(−)-**6** ester; bp 148–152° (20 mm); $[\alpha]^{25}D$ +46.5° (*c* 6.2328, MeOH), lit.[18a] $[\alpha]^{25}D$ +53.5° (EtOH); RD (*c* 0.0296, MeOH) (24–25°), $[\phi]_{325}$ +660°, $[\phi]_{300}$ +1270°, $[\phi]_{289}$ +2510, $[\phi]_{284}$ +1890° (sh), $[\phi]_{274}$ 0°, $[\phi]_{265}$ −770°, $[\phi]_{255}$ −770°, $[\phi]_{253}$ 0°, $[\phi]_{240}$ +1780°; CD (*c* 0.2960, MeOH) (24–25°), $[\theta]_{300}$ +360°, $[\theta]_{288}$ +1890°, $[\theta]_{284}$ +1730°, $[\theta]_{281}$ +2550°, $[\theta]_{274}$ +1990°, $[\theta]_{255}$ +460°, $[\theta]_{240}$ +2340°.

**Biological.**—Diets were prepared containing 0.15, 0.20, and 0.50% ester. The compounds were dissolved in 500 ml of ether and the solution was thoroughly mixed with 2.5 kg of standard Purina rat chow so as to impregnate the pellets. The ether evaporated on standing for 12 hr. Six rats (Swiss Webster) were used as a control and administered a diet free of drug. Another six rats were used for each drug at each dosage level. The rats were weighed daily. At the end of 12 days of feeding, the control as well as the experimental group consumed 2.5 kg of food per six rats. The rats were anesthetized with ether, the aorta was surgically exposed, and the blood was collected for analysis. Serum cholesterol was determined by the method of Abell, *et al.*[22]

**Acknowledgment.**—We are grateful to the National Institutes of Health for support of this work through Grant HE-08577.

(22) L. L. Abell, B. B. Lavy, B. B. Brodie, and F. E. Kendell, *J. Biol. Chem.*, **195**, 357 (1952).

## Salicylic Acid Analogs of Phenothiazine as Antiinflammatory Agents[1]

ANDREW J. SAGGIOMO[2a] AND BLAINE M. SUTTON[2b]

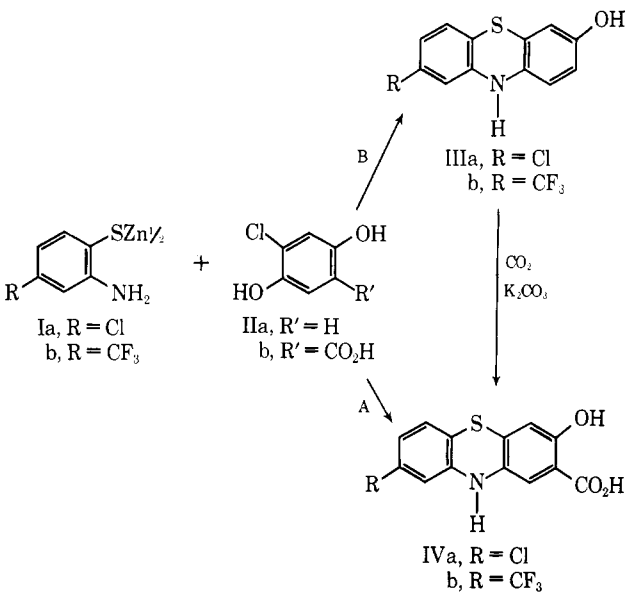
*Research Institute of Temple University, Philadelphia, Pennsylvania 19144, and Research Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101*

*Received March 18, 1968*

The potent antiinflammatory activity of 8-trifluoromethylphenothiazine-1-carboxylic acid[3] and the marked antirheumatic effects of salicylic acid and its derivatives prompted us to prepare 8-chloro- and 8-trifluoromethyl-3-hydroxyphenothiazine-2-carboxylic acids.

Although a wide variety of ring-substituted phenothiazines have been described,[4] no hydroxycarboxylic acids have been previously reported. In the course of this study, the desired 3-hydroxyphenothiazine-2-carboxylic acids were readily accessible by two paths (Scheme I). Path A involved an extension of the facile

SCHEME I




synthesis of hydroxyphenothiazines recently described

(1) These compounds were prepared at the Research Institute of Temple University under a contract with Smith Kline and French Laboratories.

(2) (a) Research Institute of Temple University; (b) Smith Kline and French Laboratories.

(3) B. M. Sutton and J. H. Birnie, *J. Med. Chem.*, **9**, 835 (1966); J. H. Birnie, B. M. Sutton, M. Zuccarello, and J. A. Rush, *Med. Pharmacol. Exp.*, **17**, 15 (1967).

(4) A review of the phenothiazine literature is presented by E. Schenker and H. Herbst, *Drug. Res.*, **5**, 269 (1963).