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°, $[\theta]_{255}$ −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]

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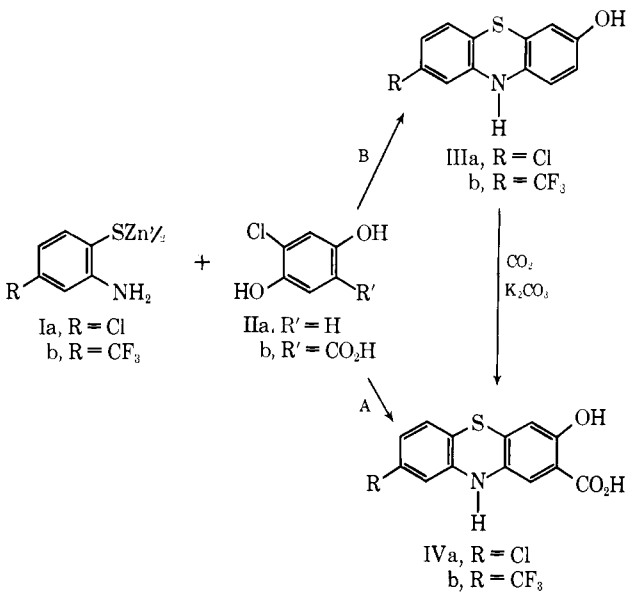
The potent antiinflammatory activity of 8-trifluoromethylphenothiazine-1-carboxylic acid[3] and the marked antirheumatic effects of salicylic acid and its derivatives prompted us to prepare 8-chloro- and 8-trifluoromethyl-3-hydroxyphenothiazine-2-carboxylic acids.

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).

by Nodiff and Hausman.[5] Condensation of the 2-aminobenzenethiol zinc salts (Ia and Ib) with 4-chloro-2,5-dihydroxybenzoic acid (IIb) provided 8-chloro- and 8-trifluoromethyl-3-hydroxyphenothiazine-2-carboxylic acids (IVa and IVb, respectively).

An alternate approach (path B) to IVa and IVb employed the Kolbe–Schmitt reaction.[6] Using Marasse's modification,[6] the carbonation of 2-chloro- (IIIa) and 2-trifluoromethyl-7-hydroxyphenothiazines (IIIb) produced the 3-hydroxyphenothiazine-2-carboxylic acids (IVa and IVb). Although two positions *ortho* to the hydroxyl group are available for carbonation, only one isomer was isolated in each case. Physical and spectral data revealed that the products from paths A and B were identical.

Compounds IVa and IVb were tested for antiinflammatory activity in two biological assays. Preliminary data indicate that these compounds possess a low order of activity. 8-Chloro-3-hydroxyphenothiazine-2-carboxylic acid (IVa) produced a significant inhibition of granuloma growth in the carrageenin filter paper granuloma assay[7] in adrenalectomized rats subcutaneously at a dose of 80 mg/kg. At a lower dose of 20 mg/kg it was without effect. The trifluoromethyl analog (IVb) was ineffective at 40 mg/kg. Phenylbutazone was effective in this assay subcutaneously at 20 mg/kg. IVa was ineffective in the ultraviolet erythema test[8] when administered orally at a dose of 40 mg/kg. The oral ED_{50} of phenylbutazone by this method was 7.4 mg/kg.

Experimental Section[9]

2-Trifluoromethyl-7-hydroxyphenothiazine (IIIb) was prepared from the zinc salt of 2-amino-4-trifluoromethylbenzenethiol[10] (Ib) and 2-chlorohydroquinone (Aldrich Chemical Co.) (IIa) using the method described in ref 5. IIIb was obtained (77%) as tan platelets (C_6H_6), mp 211–214°. *Anal.* ($C_{13}H_8F_3NOS$) C, H.

3-Hydroxyphenothiazine-2-carboxylic Acids (IVa and IVb). Method A.—A stream of O_2 was bubbled for 1 hr through a refluxing mixture of 4-chloro-2,5-dihydroxybenzoic acid[11] (0.0186 mole), NaOH (0.0372 mole) in H_2O (7 ml), and 4-chloro-2-aminobenzenethiol zinc salt (Ia, 0.0093 mole) in EtOH (50 ml). The dark brown suspension was filtered hot, and the filtrate was treated with sodium dithionite (3.2 g) in H_2O (214 ml). The yellow mixture was then heated at 40–50° for 15 min and was decanted from a small amount of gum. Overnight the decantate deposited a yellow solid[12] which on recrystallization from AcOH gave IVa, 40%, mp 277–280° dec. *Anal.* ($C_{13}H_8ClNO_3S$) C, H. Similarly, 4-trifluoromethyl-2-aminobenzenethiol zinc salt (Ib) provided IVb, 14%, mp 253–254.5° dec. *Anal.* ($C_{14}H_8F_3NO_3S$) C, H. Absorption bands of ir spectra were as expected.

Method B.—An intimate mixture of granular anhydrous potassium carbonate (107.4 g, 0.78 mole) and 2-chloro-7-hydroxyphenothiazine[5] (35.4 g, 0.14 mole) was placed in a 250-ml Hastelloy C pressure vessel. The reactor was sealed, CO_2 gas was admitted under pressure, and the vessel was vented. This procedure was carried out several times. Finally, the reactor was pressurized with CO_2 (42.2–56.2 kg/cm²), heated to 200° during 19 hr, and maintained at 200–220° for 28 hr. The pressure vessel was cooled to room temperature and vented. After extracting the reaction cake with 2.5 l. of hot H_2O, the extract was treated with carbon. Acidification of the filtrate with HCl gave a brown precipitate which on recrystallization provided IVa (18%). The 8-trifluoromethyl derivative IVb was obtained (41%) in a similar manner. Samples of IVa and IVb prepared by methods A and B gave identical ir spectra, and mixture melting points were not depressed.

Acknowledgment.—The authors are indebted to Dr. J. H. Birnie of Smith Kline and French Laboratories for the biological testing and to Miss Pauline Schwartz for her assistance with some of the experiments.

(5) E. A. Nodiff and M. Hausman, *J. Org. Chem.*, **31**, 625 (1966).

(6) A review of this reaction and its modifications is presented by A. Lindsey and H. Jeskey, *Chem. Rev.*, **57**, 583 (1957).

(7) Modification of the methods reported by R. Meier, W. Schuler, and P. Desaulles, *Experientia*, **6**, 469 (1950); and A. Tanaka, F. Kobayaski, and T. Miyake, *Endocrinol. Japan*, **7**, 357 (1960).

(8) C. Winder, J. Wax, V. Burr, M. Benn, and C. Rosiere, *Arch. Intern. Pharmacodyn.*, **116**, 261 (1958).

(9) Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Melting points were determined in open capillary tubes in an electrically heated Thiele-Dennis apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(10) A. Kiprianov and L. Yagupolskii, *Zh. Obshch. Khim.*, **22**, 2209 (1952); *Chem. Abstr.*, **47**, 4769 (1953).

(11) S. Bhattacharyya and D. Seymour, *J. Chem. Soc.*, 1139 (1950).

(12) In the case of IVb, this solid was precipitated only by the addition of AcOH.

Synthesis of 1,4-Disubstituted Piperazines. II[1]

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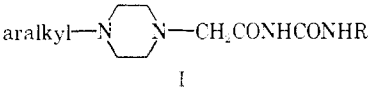
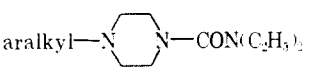
In the first paper[2] in this series, various piperazines were made having, as one substituent, an aromatic ring and, as the other, a substituted acylurea in order to obtain possible sedatives or other physiologically active compounds.

In this article, the piperazines synthesized generally contain various aralkyl groups and either acylurea substituents or substituted carbamoyl groups. Most of them are of types I and II.



I



II

Biological Data.[3]—Compound **1** was active at 100 mg but inactive at 50 mg/kg ip in affording protection to mice against electroshock when administered 30 min before the stimulus. Also, when administered 30 min previous to pentylenetetrazole **1** showed antipentylenetetrazole activity (clonic convulsions) in mice at 100 mg/kg ip but was ineffective at 50 mg.

Compound **3** was a mildly acting psychomotor stimulant (photocell count method) at 300 mg/kg *po* in mice. Compound **12** showed slight psychomotor stimulation in mice at 100 mg/kg *po*. Compound **15** was a mild psychomotor depressant at 300 mg/kg *po* and a mild stimulant at 30 mg/kg *po*. Compound **15** also showed questionable activity against a *Trichomonas gallinae* vaginal infection in hamsters at 100 mg/kg *po*. Compound **19** was a feeble stimulant at 30 mg/kg *po*,

(1) Support of this work by the Sterling-Winthrop Research Institute of Rensselaer, N. Y., is acknowledged with gratitude.

(2) M. Verderame, *J. Med. Chem.*, **9**, 153 (1966).

(3) The author is indebted to the Biological Division of the Sterling-Winthrop Research Institute for carrying out these studies.