(8) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).
(9) B. Belleau, *J. Med. Chem.*, **7**, 776 (1964).
(10) A. Korolkovas, "Essentials of Molecular Pharmacology," Wiley-Interscience, New York, N.Y., 1970, p. 191.
(11) J. M. Gulland and R. Robinson, *Nature*, **115**, 625 (1925).
(12) L. F. Small, "Chemistry of the Opium Alkaloids," U. S. Government Printing Office, Washington, D.C., 1932.
(13) M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, **74**, 1109 (1952).
(14) G. Stork, *ibid.*, **74**, 768 (1952).
(15) H. Rapoport and J. B. Lavigne, *ibid.*, **75**, 5329 (1953).
(16) H. Rapoport and G. B. Payne, *J. Org. Chem.*, **15**, 1093 (1950).
(17) H. Rapoport and G. B. Payne, *J. Am. Chem. Soc.*, **74**, 2630 (1952).
(18) A. K. Bose, *Chem. Ind.*, **1954**, 130.
(19) J. M. Lindsey and W. H. Barnes, *Acta Crystallogr.*, **8**, 227 (1955).
(20) M. Mackay and D. C. Hodgkin, *J. Chem. Soc.*, **1955**, 3261.
(21) J. Kalvoda, P. Buchschacher, and O. Jeger, *Helv. Chim. Acta*, **38**, 1847 (1955).
(22) L. Gylbert, *Acta Crystallogr.*, **B29**, 1630 (1973).
(23) G. Kartha, F. R. Ahmed, and W. H. Barnes, *ibid.*, **15**, 326 (1962).
(24) H. VanKoningsveld, *Rec. Trav. Chim. Pays-Bas*, **89**, 375 (1970).
(25) G. Kartha, F. R. Ahmed, and W. H. Barnes, *Acta Crystallogr.*, **13**, 525 (1960).
(26) F. R. Ahmed, W. H. Barnes, and L. Masironi, *ibid.*, **16**, 237 (1963).
(27) C. K. Johnson, ORTEP, Report ORNL-3794, Oak Ridge National Laboratories, Oak Ridge, Tenn., 1965.
(28) J. J. Kaufman, E. Kerman, and W. S. Koski, *Int. J. Quantum Chem., Quantum Biol. Symp.*, **1**, 289 (1974).
(29) P. S. Portoghese, *Ann. Rev. Pharmacol.*, **10**, 51 (1970).

ACKNOWLEDGMENTS

Abstracted in part from a dissertation submitted by T. L. Breon to the Graduate School, University of Rhode Island, in partial fulfillment of the Doctor of Philosophy degree requirements.

Potential Hypocholesteremic Derivatives of Styrylacetic Acid II: *cis*- and *trans*-3-Methyl-4-phenyl-3-butenoic Acid Analogs

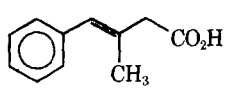
E. S. STRATFORD *[x], L. M. SMITH [1], and G. W. TOMECKO [1]

Received December 20, 1976, from the *Section of Medicinal Chemistry and Pharmacognosy, School of Pharmacy, University of Connecticut, Storrs, CT 06268.* Accepted for publication April 7, 1977. *Present address: School of Pharmacy, West Virginia University Medical Center, Morgantown, WV 26505.

Abstract □ The synthesis and preliminary biological testing for *in vitro* cholesterol biosynthesis inhibitory activity of 2-indeneacetic acid, 2-methyl-1,2-dihydro-2-naphthoic acid, and their 5- and 7-chloro derivatives, respectively, are described. These compounds were prepared as *trans*- and *cis*-analogs of the known antilipemic agent 3-methyl-4-phenyl-3-butenoic acid. Although both series of compounds showed cholesterol biosynthesis inhibitory properties, chloro substitution enchanced potency only in the *cis*-system. These findings are discussed in terms of a possible relationship between the *cis*-compounds and clofibrate-type antilipemic agents.

Keyphrases □ *cis*- and *trans*-3-Methyl-4-phenyl-3-butenoic acid analogs—synthesized, evaluated for effect on cholesterol biosynthesis in rat liver homogenates □ 2-Indeneacetic acid and 5-chloro derivative—synthesized, evaluated for effect on cholesterol biosynthesis in rat liver homogenates □ 2-Naphthoic acids, substituted—synthesized, evaluated for effect on cholesterol biosynthesis in rat liver homogenates □ Cholesterol biosynthesis—effect of 2-indeneacetic acid and substituted 2-naphthoic acids and chloro derivatives, rat liver homogenates □ Structure–activity relationships—effects of 2-indeneacetic acid and substituted 2-naphthoic acids and chloro derivatives on cholesterol biosynthesis in rat liver homogenates

In continuing investigations (1) of the structure–activity relationships for cholesterol biosynthesis inhibition by compounds related to 3-methyl-4-phenyl-3-butenoic acid (benzalbutyric acid) (I), the influence of the double bond stereochemistry on biological activity was examined. Compound I exists in the (*E*)-configuration (2), but it has not been established that this configuration represents the optimal geometry for biological action.



I

In an initial attempt to obtain information relating to this question, the synthesis of indeneacetic acids (II*a* and II*b*) and dihydronaphthoic acids (III*a* and III*b*) as *trans*- and *cis*-congeners of the parent system was undertaken. Although these compounds also differ with respect to the α-carbon substitution pattern, they were believed to be useful as initial probes. This report describes their synthesis and preliminary *in vitro* testing.

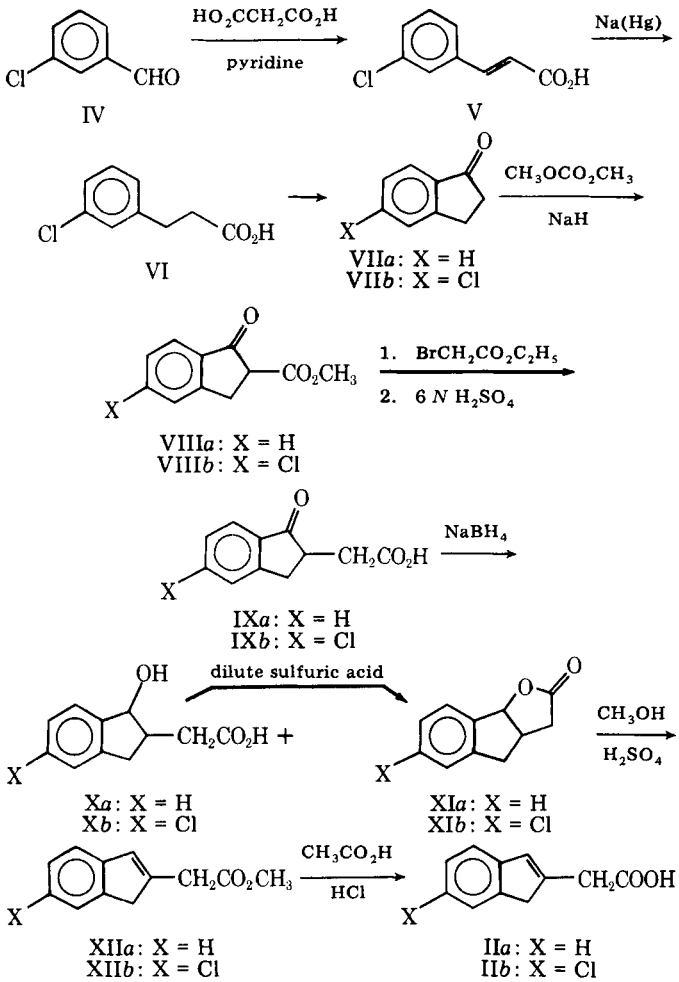
DISCUSSION

The synthesis of II*a* and II*b* is outlined in Scheme I (also see *Experimental*). Although the mixture of hydroxy acid X and lactone XI could be converted entirely into the lactone by prolonged stirring in dilute sulfuric acid, for preparative runs it was more convenient to use the mixture directly for the subsequent reaction.

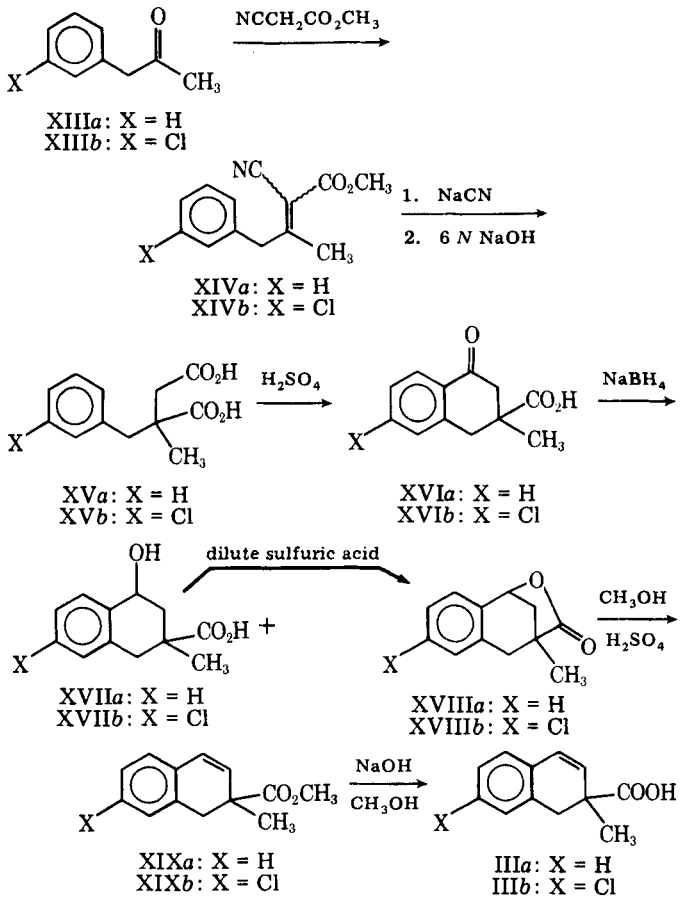
Synthesis of the *cis*-analogs was accomplished according to the sequence outlined in Scheme II.

Interestingly, if the methanolysis of XVIII or the mixture of XVII and XVIII was terminated after refluxing for only 4 hr and the product was saponified, methoxy acid XX could be obtained from the reaction product mixture. This finding is in agreement with the suggestion advanced previously (3) that methanolyses of similar tricyclic lactones, including XI, proceed *via* an intermediate benzyl carbonium ion. This conclusion was based largely on the fact that methanolysis of γ-phenylbutyrolactone afforded methyl 4-methoxy-4-phenylbutanoate instead of the anticipated

[1] Undergraduate research participant.



Scheme I



Scheme II

β,γ-unsaturated ester. This report (3) suggested that the methoxy compound was produced because substitution by methoxide occurred in preference to elimination, as in the tricyclic lactones. The results obtained in the present case, however, imply that the γ-methoxy esters either are intermediates in the formation of the β,γ-unsaturated esters or, more likely, are in equilibrium with the benzyl carbonium ion since none of the methoxy acid was detected when the methanolysis was allowed to continue for 24 hr.

EXPERIMENTAL[2]

2-Indeneacetic Acid (IIa)—Compound II*a* was prepared as described previously (3), affording slightly yellow flakes from 20% aqueous acetic acid, mp 122–123° [lit. (3) mp 124–125°].

Anal.—Calc. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.79; H, 5.70.

5-Chloro-1-indanone (VII*b*)—Compound VII*b* was prepared as described previously (4) from *m*-chlorobenzaldehyde (5) and sublimed at 80°, affording white crystals, mp 72–88°, apparently as a mixture of keto and enol forms since the material appeared chromatographically (TLC) and spectroscopically pure. Crystallization from ethyl acetate afforded colorless crystals, mp 93–95° [lit. (4) mp 100°].

Anal.—Calc. for C_9H_7ClO: C, 64.88; H, 4.23; Cl, 21.28. Found: C, 64.66; H, 4.32; Cl, 21.56.

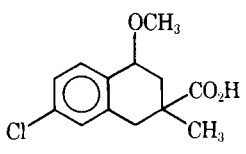
5-Chloro-2-methoxycarbonyl-1-indanone (VIII*b*)—According to the method of House and Hudson (6), a solution of 8.0 g (48 mmoles) of VII*b* in 65 ml of sodium-dried benzene was added dropwise over 2 hr to a mixture of 34 ml of dimethyl carbonate and 3 equivalents of sodium hydride (6.91 g of a 50% dispersion in mineral oil) in 85 ml of benzene at 85°. Heating was continued for 2 hr after the complete addition. The mixture was then cooled at 15° and acidified with 15 ml of acetic acid.

The resulting mixture was poured onto ice–hydrochloric acid, and the organic phase was washed successively with saturated sodium bicarbonate and brine and then dried. The solvent was removed *in vacuo*, affording a dark-green oil. The oil was distilled with the aid of a heat lamp to prevent crystallization in the distilling head. The distillate was recrystallized from hot hexane after treatment with charcoal, affording 5.2 g (48%) of VIII*b* as white crystals, mp 83–84°.

Anal.—Calc. for $C_{11}H_9ClO_3$: C, 58.81; H, 4.04; Cl, 15.78. Found: C, 58.37; H, 4.09; Cl, 15.41.

5-Chloro-1-indanone-2-acetic Acid (IX*b*)—A mixture of 6.0 g (26.7 mmoles) of VIII*b*, 5.5 g (33 mmoles) of ethyl bromoacetate, and 3.8 g (37.6 mmoles) of triethylamine in 300 ml of sodium-dried ether was heated at reflux for 24 hr. The solvent was removed *in vacuo*, and 375 ml of 6 *N* H_2SO_4 was added. The resulting mixture was heated at reflux overnight. The reaction mixture was allowed to cool and was then extracted with ether.

The ether solution was extracted several times with saturated sodium bicarbonate solution, and the combined bicarbonate extracts were acidified with dilute sulfuric acid. The precipitate was isolated and dried in a heated vacuum desiccator, affording 4.6 g (77%) of crude IX*b* as a



XX

[2] Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., or by Baron Consulting Co., Orange, Conn. IR spectra were recorded on a Beckman Acculab 3 spectrophotometer. NMR spectra were obtained with a Hitachi Perkin-Elmer model R-24 spectrometer, using tetramethylsilane as the internal standard. In all cases, the spectra obtained were consistent with proposed structures.

For biological evaluations, ^{14}C-counting was performed with a Packard Tri-Carb liquid scintillation spectrometer, model 3375. Where unspecified, organic solutions were dried prior to evaporation of the solvent with either anhydrous sodium sulfate or anhydrous magnesium sulfate. Brine refers to a saturated solution of sodium chloride.

colorless solid, mp 158–161°. Recrystallization from ethyl acetate afforded an analytical sample, mp 162–163°.

Anal.—Calc. for $C_{11}H_9ClO_3$: C, 58.81; H, 4.04; Cl, 15.78. Found: C, 58.40; H, 4.22; Cl, 15.94.

5-Chloro-1-hydroxy-2-indaneacetic Acid Lactone (XI*b*)—To a solution of IX*b* (2.5 g, 11.1 mmoles) in 90 ml of 2 *N* NaOH was added 0.41 g (11.1 mmoles) of sodium borohydride. The solution was allowed to stir at room temperature for 24 hr and was then acidified with 4 *N* H_2SO_4.

The resulting mixture was extracted with ether, the organic phase was dried, and the solvent was removed *in vacuo*, affording 2.19 g of white solid as a mixture of X*b* and XI*b*. The mixture was then stirred in 200 ml of 4 *N* H_2SO_4 for 3 days, and the solid was filtered and dried *in vacuo*, affording 2.04 g (89%) of XI*b*, mp 111–114°. Recrystallization from heptane–ethyl acetate afforded an analytical sample, mp 119.5–121°.

Anal.—Calc. for $C_{11}H_9ClO_2$: C, 63.32; H, 4.35; Cl, 16.99. Found: C, 63.06; H, 4.45; Cl, 17.00.

5-Chloro-2-indeneacetic Acid (II*b*)—A solution of XI*b* (1.62 g, 7.77 mmoles) in 50 ml of methanol containing 1 ml of concentrated sulfuric acid was heated at reflux for 18 hr. The cooled solution was diluted with 100 ml of ether and washed with 100 ml of distilled water. The aqueous layer was extracted with 100 ml of ether, and the combined organic layers were washed successively with 100 ml of saturated sodium bicarbonate and brine.

The resulting solution was dried, and the solvent was removed *in vacuo*, affording a yellow-orange oil. The oil was dissolved in 100 ml of acetic acid–concentrated hydrochloric acid (4:1) and heated on a steam bath for 2 hr. The cooled reaction mixture was poured onto 300 g of ice. The precipitate was isolated and dried, affording 1.16 g (72%) of crude product, mp 129–132°. Recrystallization from heptane–ethyl acetate afforded pure II*b*, mp 134.5–136°.

Anal.—Calc. for $C_{11}H_9ClO_2$: C, 63.32; H, 4.35; Cl, 16.99. Found: C, 63.47; H, 4.28; Cl, 16.85.

2-Benzyl-2-methylsuccinic Acid (XV*a*)—Compound XV*a* was prepared as described by Foucaud (7), affording a white powder, mp 140–142° [lit. (7) mp 144°].

Anal.—Calc. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.24; H, 6.43.

2-Methyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (XVI*a*)—A mixture of 5.8 g (26.1 mmoles) of diacid XV*a* and 50 ml of concentrated sulfuric acid was stirred at 45–50° for 4 hr. The cooled mixture was poured onto ice (300 g) and extracted with ether (3 × 100 ml). The combined ether extracts were washed with brine and dried, and the solvent was evaporated. Recrystallization of the solid residue from ethyl acetate afforded 4.1 g (78%) of XVI*a* as white crystals, mp 163–166°. A further recrystallization afforded an analytical sample, mp 172.5–174.5°.

Anal.—Calc. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.56; H, 6.08.

2-Methyl-1,2-dihydro-2-naphthoic Acid (III*a*)—To a solution of XVI*a* (20.4 g, 0.1 mole) in 300 ml of 2 *N* NaOH was added 3.8 g (0.1 mole) of sodium borohydride, and the solution was allowed to stir at room temperature. After 24 hr, the solution was acidified by dropwise addition of 4 *N* H_2SO_4 and was then extracted with ether. The ether extract was washed with brine and dried, and the solvent was removed *in vacuo*, affording 19.5 g of a mixture of XVII*a* and XVIII*a* in an undetermined ratio. Without further purification, the mixture was dissolved in 500 ml of methanol, and 5 ml of concentrated sulfuric acid was added.

The resulting solution was heated at reflux for 30 hr, cooled to room temperature, and concentrated *in vacuo* to about 60% of the original volume. The concentrate was then partitioned between 250 ml each of ether and distilled water. The aqueous phase was removed and extracted with 3 × 150 ml of ether, and the combined organic layers were washed with brine and dried. Evaporation of the solvent afforded 20 g of crude XIX*a* as a yellow-orange liquid. Although the procedure was not performed routinely, the hydroxy acid XVII*a* could be isolated from the crude mixture by crystallization from ethyl acetate as colorless crystals, mp 181–183°.

Anal.—Calc. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.75; H, 6.86.

Lactone XVIII*a* was obtained by evaporating the filtrate, redissolving in ether, and washing with saturated sodium bicarbonate solution. The remaining ether solution was dried, and the solvent was evaporated. Recrystallization of the residue from hexane afforded pure XVIII*a*, mp 86.5–87.5°.

Anal.—Calc. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.37; H, 6.35.

Crude XIX*a* was dissolved in 450 ml of methanol, and 16.5 g (0.25 mole) of 85% potassium hydroxide was added. The solution was refluxed for 12 hr, cooled, concentrated *in vacuo* to about 100 ml, and diluted with 200 ml of distilled water. The resulting aqueous solution was washed with 3 × 100 ml of ether and acidified with 4 *N* H_2SO_4. The resulting mixture was extracted with 3 × 100 ml of ether, and the combined ether extracts were washed with brine and dried. The solvent was then removed *in vacuo*, affording 16.8 g (89% overall from XVI*a*) of crude III*a* as a slightly yellow solid, mp 89–92°. Recrystallization from hexane afforded pure III*a*, mp 93–94.5°.

Anal.—Calc. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.72; H, 6.51.

4-Methoxy-2-methyl-1,2,3,4-tetrahydro-2-naphthoic Acid (XX)—A solution of 5.0 g of XVIII*a* in 50 ml of methanol was refluxed for 4 hr and worked up as described above to give 5.1 g of a cloudy liquid. Distillation (105–115°/0.6 mm) afforded 4.7 g of an impure oil. A 3.0-g portion of this material was refluxed for 2.5 hr in a mixture of 15 ml of methanol and 15 ml of 2 *N* NaOH. Workup gave 2.7 g of a viscous oil, which was dissolved in hot hexane. The solution was allowed to stand at room temperature overnight, and 0.5 g of a white solid, mp 142–145°, was isolated. A further recrystallization from hexane afforded pure XX, mp 145–147°.

Anal.—Calc. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.71; H, 7.48.

Methyl 2-Cyano-4-(3′-chlorophenyl)-3-methyl-2-butenoate (XIV*b*)—A mixture of 26.0 g (0.154 mole) of *m*-chlorophenylacetone (8), 19.1 g (0.193 mole, 1.25 equivalents) of methyl cyanoacetate, 0.5 ml of piperidine, and 0.5 ml of acetic acid in 100 ml of sodium-dried benzene was refluxed for 18 hr; water was collected in a Dean–Stark trap. The reaction mixture was allowed to cool to room temperature; it was then diluted with 200 ml of ether and washed successively with 100-ml portions of distilled water, saturated sodium bicarbonate, brine, 3 *N* HCl, and brine.

The resulting solution was dried, and the solvent was removed *in vacuo*. Distillation of the residue afforded 32.6 g (85%) of XIV*b* as a slightly yellow liquid, bp 138–148°/0.3 mm. This liquid was shown to be approximately a 1:1 mixture of (*E*)- and (*Z*)-isomers by NMR analysis, with the methyl groups appearing as sharp singlets at δ 2.14 and 2.25 ppm, the methoxyl protons appearing at δ 3.80 and 3.83 ppm, the methylene protons appearing at δ 3.83 (shoulder on methoxyl resonance) and 4.13 ppm, and the aromatic protons appearing as a multiplet centered at δ 7.18 ppm. No attempts were made to purify the material further or to separate the isomers.

2-(3′-Chlorobenzyl)-2-methylsuccinic Acid (XV*b*)—A solution of 5.0 g (0.020 mole) of XIV*b* in 50 ml of absolute ethanol was warmed to about 60° and 3.4 ml of 50% aqueous potassium cyanide was added. The mixture was heated at reflux for 18 hr, and 50 ml of 6 *N* NaOH was added. The ethanol was removed by distillation, and the resulting mixture was refluxed an additional 12 hr. The cooled reaction mixture was poured into ice–sulfuric acid (300 g, 30 ml) and extracted with ether.

The organic solution was then washed with brine and dried. The solvent was then removed *in vacuo*, leaving a viscous oil which crystallized from benzene–heptane, affording 4.6 g (89%) of crude XV*b*, mp 138–143°. Recrystallization from benzene afforded white crystals, mp 144–146°.

Anal.—Calc. for $C_{12}H_{13}ClO_4$: C, 56.15; H, 5.10; Cl, 13.81. Found: C, 55.80; H, 4.90; Cl, 14.14.

7-Chloro-2-methyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (XVI*b*)—A solution of 5.80 g (22.6 mmoles) of XV*b* in 60 ml of concentrated sulfuric acid was stirred at 50° for 3 hr. The resulting solution was poured onto ice (300 g); the precipitate was filtered and dried, affording 4.6 g (85%) of crude product, mp 158–162°. Recrystallization from ethyl acetate afforded pure XVI*b* as colorless crystals, mp 163–165°.

Anal.—Calc. for $C_{12}H_{11}ClO_3$: C, 60.39; H, 4.65; Cl, 14.86. Found: C, 60.29; H, 4.58; Cl, 15.04.

7-Chloro-4-hydroxy-2-methyl-1,2,3,4-tetrahydro-2-naphthoic Acid Lactone (XVIII*b*)—To a solution of 1.07 g (4.5 mmoles) of XVI*b* in 50 ml of 2 *N* NaOH was added 0.17 g (4.5 mmoles) of sodium borohydride. After 24 hr, the solution was acidified and extracted with ether (3 × 50 ml). The combined organic layers were washed with brine and dried, and the solvent was removed *in vacuo*. The resulting solid was stirred for 4 days in 4 *N* H_2SO_4 at room temperature, filtered, and dried, affording 0.93 g (93%) of the crude lactone, mp 102–105°. Recrystallization from ethyl acetate afforded pure XVI*b*, mp 105–106°.

Anal.—Calc. for $C_{12}H_{11}ClO_2$: C, 64.73; H, 4.98. Found: C, 64.43; H, 4.63.

7-Chloro-2-methyl-1,2-dihydro-2-naphthoic Acid (III*b*)—A solution of 2.0 g (9.0 mmoles) of XVIII*b* in 50 ml of methanol containing 1 ml of concentrated sulfuric acid was heated at reflux for 18 hr. The cooled solution was diluted with 100 ml of ether and washed with 100 ml

Table I—Effect of Compounds on Incorporation of 2-^{14}C-Acetate into Neutral Sterols by Rat Liver Homogenate Preparations

Compound	Concentration, m*M*	Percent Incorporation[a]
I	10	6.7 ± 0.51[c]
	1	40.9 ± 0.95
	0.5	54.4 ± 2.00
	0.1	72.7 ± 9.90
II*a*	10	8.1 ± 1.85
	5	18.9 ± 1.65
	1	64.1 ± 2.03
	0.5	75.0 ± 2.08
II*b*	10	1.8 ± 0.57
	5	7.8 ± 4.06
	1	60.3 ± 1.01
	0.5	85.9 ± 1.34
III*a*	10	20.8 ± 2.62
	5	54.3 ± 2.11
	1	95.9 ± 6.72
	0.5	106.9 ± 3.72
III*b*	10	0.7 ± 0.17
	5	6.2 ± 3.35
	1	57.7 ± 6.91
	0.5	66.8 ± 2.91

[a] Relative to incorporation in controls being defined as 100%. [b] Data taken from Ref. 1. [c] Standard error of mean of three experiments.

of distilled water. The aqueous layer was extracted with 100 ml of ether, and the combined organic layers were washed with 100-ml portions of saturated sodium bicarbonate and brine and dried. The solvent was evaporated *in vacuo*.

The resulting oil was dissolved in 50 ml of methanol and 1.2 g of potassium hydroxide. The solution was allowed to reflux overnight and acidified with 100 ml of 2 *N* H_2SO_4. The mixture was then extracted with 2 × 100 ml of ether. The combined extracts were washed with brine and dried. The solvent was then removed *in vacuo*, affording 1.74 g (87%) of crude product, mp 132–135°. Recrystallization from heptane gave pure III*b*, mp 138–140°.

Anal.—Calc. for $C_{12}H_{11}ClO_2$: C, 64.73; H, 4.98; Cl, 15.92. Found: C, 64.52; H, 5.30; Cl, 16.20.

RESULTS

Compounds II*a*, II*b*, III*a*, and III*b* were examined for their ability to inhibit the incorporation of 2-^{14}C-acetate into nonsaponifiable sterols by rat liver homogenates using the method described previously (1) (Table I).

In the unsubstituted compounds, the *trans*-analog II*a* is considerably more potent than the *cis*-III*a*, as was anticipated. However, the effect of *para*-substitution in the two systems is quite different. Incorporation of the chloro group in the *trans*-system, on the other hand, produced a marked increase in potency.

The variable response observed for the two systems cannot be accounted for on the basis of available information since several alternative explanations are possible. From among those possible, however, certain rationalizations readily lend themselves to further examination by extension of the series of compounds employed in this study.

On the basis of earlier studies with acyclic analogs of I (1), it was anticipated that chloro substitution *para* to the point of attachment of the double bond would enhance potency, especially in the *trans*-system, which is structurally more closely related to the acyclic analogs. However, this effect was demonstrated only for compounds in which the carbon alpha to the carboxyl group is tetrasubstituted. Previously, it was suggested that the apparent reduction in potency resulting from *p*-chloro substitution in I (9) might be due to contamination of material with the less active β,γ-unsaturated isomer. In view of the results reported herein, such an explanation is less attractive. These observations would, however, be consistent with the suggestion that the mode of action depends on the substitution pattern at the α-carbon atom. The synthesis of additional analogs that should help clarify the situation is currently in progress.

The difference in the effect of substitution in the two systems also allows an interesting interpretation on the basis of geometrical properties. One original goal of this research program was to obtain information that could be used in relation to the speculation that I and 2-(4′-chlorophenoxy)-2-methylpropanoic acid (XXI), the active metabolite of clofibrate, might be affecting cholesterol biosynthesis by similar mechanisms. Examination of Dreiding models of II*a*, II*b*, III*a*, III*b*, and XXI reveals that only the *cis*-compounds can adopt conformations in which the distance between the center of the aromatic ring and the carboxyl group is similar to that possible for XXI. The interatomic distances between the centroid of the aromatic ring and the carboxyl carbon as measured using Dreiding models fall in the possible ranges of 3.5–4.9 Å for XXI, 4.2–5.3 Å for III*a* and III*b*, and 5.8 Å for II*a* and II*b*. Furthermore, it is known that removal of the chloro substituent in XXI and its analogs lowers their potency as inhibitors of cholesterol biosynthesis (10, 11). It seems possible, therefore, that III*a* and III*b* may be interacting with the same receptor site(s) as XXI. The additional analogs currently being prepared should provide additional information for assessing these and other possible explanations.

REFERENCES

(1) E. S. Stratford, *J. Med. Chem.*, **18**, 242 (1975).

(2) S. G. Boots, M. R. Boots, and K. E. Guyer, *J. Pharm. Sci.*, **60**, 614 (1971).

(3) S. K. Dasgupta, S. R. Ghosh, and A. S. Sarma, *Tetrahedron Lett.*, **1969**, 2331.

(4) L. Novak and M. Protiva, *Coll. Czech. Chem. Commun.*, **27**, 2413 (1962).

(5) K. C. Pandya and R. B. Pandya, *Proc. Indian Acad. Sci.*, **14A**, 112 (1941).

(6) H. O. House and C. B. Hudson, *J. Org. Chem.*, **35**, 647 (1970).

(7) A. Foucaud, *Bull. Soc. Chim. Fr.*, 873 (1963).

(8) K. L. Nelson, J. C. Robertson, and J. J. Duvall, *J. Am. Chem. Soc.*, **86**, 684 (1964).

(9) U. Valcavi and L. Gaudenzi, *Farmaco, Ed. Sci.*, **16**, 571 (1961).

(10) D. T. Witiak, T. C.-L. Ho, R. E. Hackney, and W. E. Connor, *J. Med. Chem.*, **11**, 1086 (1968).

(11) D. T. Witiak, E. S. Stratford, R. Nazareth, G. Wagner, and D. R. Feller, *ibid.*, **14**, 758 (1971).

ACKNOWLEDGMENTS

Supported by Grant HL 14950 from the National Institutes of Health.