reaction by the addition of 10% HCl (100 mL) at 0 °C gave a mixture, which was extracted into petroleum ether (2 × 250 mL). The organic extracts were combined, washed with saturated brine (4 × 50 mL), dried ($MgSO_4$), and evaporated to provide a liquid (7.4 g), which was distilled to give **22**; bp 133–134 °C (20 mm) (5.2 g, 75%). NMR δ 0.70–1.00 (9 H, m), 1.03–1.37 (2 H, m), 1.40–1.77 (6 H, m).

The following acid chlorides were prepared by heating the acid and 2 equiv of thionyl chloride at 100 °C for 2 h and purified by distillation.

2,2-Dimethylbutyryl chloride: bp 130–134 °C; yield 76%; NMR δ 0.83 (3 H, t, J = 7 Hz), 1.20 (6 H, s), 1.60 (2 H, q, J = 7 Hz).

2-Ethyl-2-methylbutyryl chloride: bp 155–158 °C; yield 61%; NMR δ 0.90 (6 H, t, J = 7 Hz), 1.20 (3 H, s), 1.43–1.97 (4 H, m).

2,2-Diethylbutyryl chloride: bp 65–66 °C (20 mm); yield 90%; NMR δ 0.83 (9 H, t, J = 7 Hz), 1.70 (6 H, t, J = 7 Hz).

2,2-Diethylpentanoyl chloride: bp 80–81 °C (20 mm); yield 92%; NMR 0.73–1.00 (9 H, m), 1.10–1.43 (2 H, m), 1.53–1.87 (6 H, m).

Isolation of HMG-CoA reductase was carried out as previously described.[16]

HMG-CoA Reductase Inhibition Assay. IC_{50} values were determined with use of five levels of each inhibitor in the assay slightly modified from that previously described.[4] In the revised protocol, enzyme was incubated for 5 min with inhibitor and NADPH prior to initiating the reaction with [^{14}C]HMG-CoA (12.5 μM, 5.9 μCi/μmol). IC_{50} values were calculated from percent inhibitions.

Acknowledgment. We are indebted to Drs. R. F. Hirschmann and E. H. Cordes for their encouragement throughout the course of this investigation, to Dr. W. C. Randall and staff for analytical support, to Dr. D. W. Cochran for NMR spectra, and to M. Z. Banker for manuscript preparation.

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3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 5. 6-(Fluoren-9-yl)- and 6-(Fluoren-9-ylidenyl)-3,5-dihydroxyhexanoic Acids and Their Lactone Derivatives

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A limited study was conducted to determine the biological consequences of rendering the phenyl rings of the previously reported[1] 7-(3,5-disubstituted [1,1′-biphenyl]-2-yl)-3,5-dihydroxy-6-heptenoic acids coplanar. Such constraint substantially diminished intrinsic HMG-CoA reductase inhibitory activity.

In a previous paper[1] on HMG-CoA reductase inhibitors, we reported the syntheses and biological properties of a series of 7-(3,5-disubstituted [1,1′-biphenyl]-2-yl)-3,5-dihydroxy-6-heptenoic (and heptanoic) acids and their δ-lactones. In this paper, we describe the syntheses and biological consequences of rendering the two phenyl groups of the 1,1′-biphenyl fragment coplanar. The rationale for such a study is the observation that the intrinsic HMG-CoA reductase inhibitory potency of unsubstituted fluorenylidene **1** (from part 1)[2] is slightly greater than that of unsubstituted biphenyl **2** (from part 2).[3] From those substituted biphenyl compounds in part 3 of this series,[1] compounds **3–5** were chosen for determining the effects of these constraints. The inherent difficulty in elaborating the dichlorofluorenylidene compound corresponding to biphenyl **3** compelled us to prepare the analogous dimethyl compound (**8**). We showed previously[1,3] that analogous methyl-for-chlorine replacement on the central phenyl ring produces little, if any, lowering of intrinsic inhibitory potency.

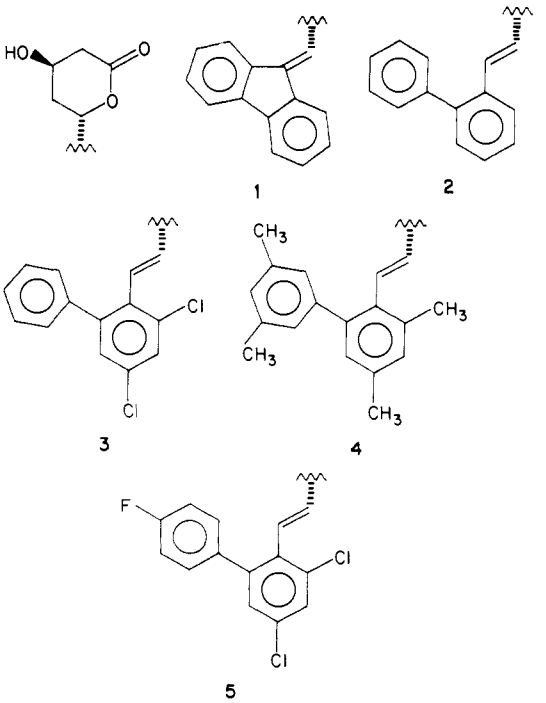

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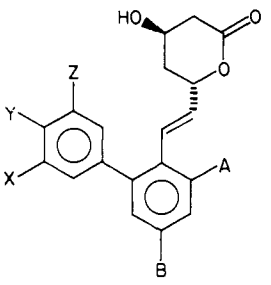
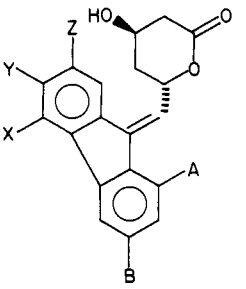
Table I. Physical Properties and in Vitro HMG-CoA Reductase Inhibitory Activities of Biphenyl Lactones I and Fluorenylidine Lactones II



I

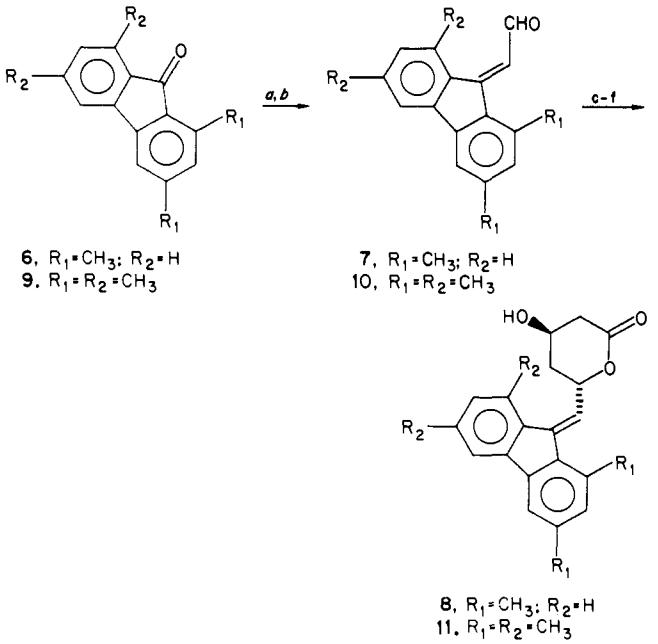


II

no.	type	A	B	X	Y	Z	recryst solvent	mp, °C	formula[b]	IC_{50},[a] μM	relative potency[c]
2	I	H	H	H	H	H	Et_2O	90–92	$C_{19}H_{18}O_3$	3.0	0.63
1	II	H	H	H	H	H	*n*-BuCl	151–152	$C_{19}H_{16}O_3$	0.89	1.5
3	I	Cl	Cl	H	H	H	*n*-BuCl/hexane	113–115	$C_{19}H_{16}Cl_2O_3$	0.08	26
8	II	CH_3	CH_3	H	H	H	*n*-BuCl	158–159	$C_{21}H_{20}O_3$	0.75	1.9
4	I	CH_3	CH_3	CH_3	H	CH_3	hexane	109–110	$C_{23}H_{26}O_3$	0.015	80
11	II	CH_3	CH_3	CH_3	H	CH_3	*n*-BuCl	155–157	$C_{23}H_{24}O_3$	0.83	1.7
5	I	Cl	Cl	H	F	H	*n*-BuCl	153–154	$C_{19}H_{15}Cl_2FO_3$	0.024	100
17	II[d]	Cl	Cl	H	F	H	*n*-BuCl	186–189	$C_{19}H_{15}Cl_2FO_3$	0.085	14

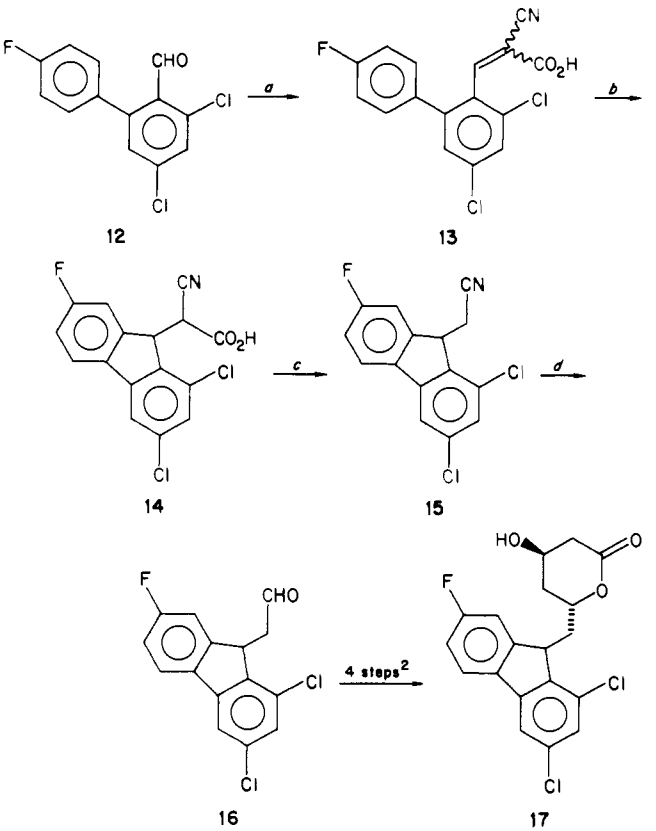
[a] Based on a single determination. [b] Analytical results are within ±0.4% of the theoretical values. [c] Potency of compactin arbitrarily assigned a value of 100; see part 1.[2] [d] Double bond is reduced, a similar reduction in the 3,5-disubstituted biphenyl series (I) results in a 0.5-4 fold loss of activity.[1]

Scheme I



[a] *n*-$Bu_3SnCH{=}CHOEt$, *n*-BuLi. [b] H_3O^+. [c] $^-CH_2CO^-CHCO_2CH_3$. [d] $NaBH_4$. [e] OH^-; H_3O^+. [f] $C_6H_5CH_3$, Δ.

Scheme II



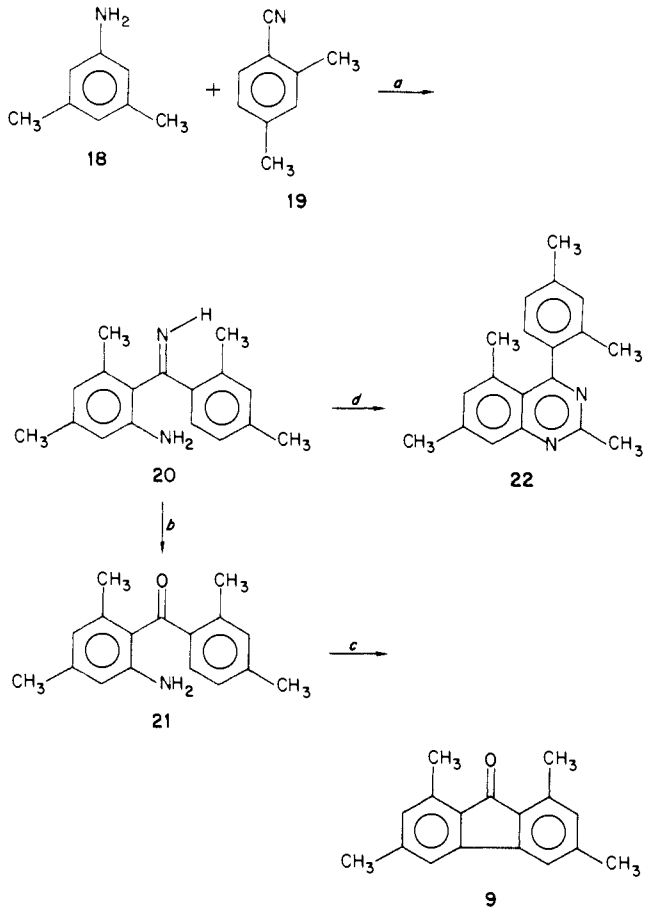
[a] $NCCH_2CO_2H$, c-C_4H_9N, HOAc, $C_6H_5CH_3$, Δ. [b] $AlCl_3$. [c] Isoquinoline, $Cu(OAc)_2$, Δ. [d] Dibal.

Chemistry. The compounds prepared for this study are listed in Table I, and their syntheses are outlined in Schemes I and II. The 6-substituted 4-hydroxypyran-2-ones were synthesized from the corresponding aldehydes via condensation with the dianion of methyl acetoacetate followed by borohydride reduction, hydrolysis, and lactonization as described in part 1.[2] The characterization of the trans isomer was based on the chemical shift of the C-6 and the coupling constants of the C-4 protons in the NMR as described in part 2.[3] Attempts to reduce the fluorenylidene lactones to their corresponding fluorenyl lactones were unsuccessful (5% Rh/C).

The synthesis of the required fluorenylidene acetaldehydes was accomplished by condensation of the analogous fluorenone with lithium ethoxyethylene (Scheme I) in the manner described in part 1.[2]

Knoevenagel condensation of **12** with cyanoacetic acid in refluxing toluene yielded 2-cyanoacrylic acid **13** instead of the expected decarboxylated acrylonitrile. Intramolecular Friedel–Crafts alkylation followed by a copper/isoquinoline-catalyzed decarboxylation formed fluorenylacetonitrile **15**, which was subsequently reduced with diisobutylaluminum hydride (Dibal) to provide **16**, the re-

Scheme III



[a] BCl_3, $AlCl_3$. [b] H_2O, HCl, Δ. [c] HNO_2. [d] H_2O, HCl, HOAc, Δ.

quisite aldehyde for lactone **17** (Scheme II).

Scheme III delineates the preparation of symmetrical fluorenone **9** from aniline **18**. A boron trichloride-mediated acylation[4] of **18** with nitrile **19** yielded imine **20**, which then was hydrolyzed in dilute HCl to afford benzophenone **21**. Interestingly, if acetic acid (40% v/v) was used as a cosolvent in the hydrolysis, only quinazoline **22** was formed. Pschorr ring closure of **21** provided **9**.

Pharmacology. The compounds listed in Table I were evaluated as their ring-opened sodium dihydroxy carboxylate forms for their ability to inhibit solubilized, partially purified rat liver HMG-CoA reductase. Contrary to the enhanced potency attending ring fusion in the unsubstituted case (**1** vs. **2**), similar ring fusion of substituted biphenyls afforded products that were substantially less potent inhibitors. It thus becomes apparent that a dihedral angle between the two phenyl rings must be greater than 0° to maintain a high level of inhibitory potency.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point aparatus and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ (unless noted otherwise) on an EM-390 spectrometer. The sole ^{13}C NMR spectrum was recorded in $CDCl_3$ on a CFT-20 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as the internal standard. Elemental analysis for carbon, hydrogen, and nitrogen were determined with a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of theory unless noted otherwise.

***trans*-6-[(9*H*-Fluoren-9-yl- or -9-ylidene)methyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-ones.** These compounds (**8**, **11**, **17**) were prepared from the corresponding aldehydes (**7**, **10**, **16**) by the general method described in ref 2; their physical/biological properties are listed in Table I.

(*E*)-(1,3-Dimethyl-9*H*-fluoren-9-ylidene)acetaldehyde (7). This compound was prepared by the general aldehyde homologation procedure described in ref 2, starting from **6**[5] (2.2 g, 10.6 mmol), yield 40% after initial chromatography (silica gel, CH_2Cl_2, R_f 0.40), and two crystallizations from cyclohexane to remove a small amount (ca. 10%) of the *Z* isomer; mp 145–145.5 °C; NMR δ 2.3 (3 H, s), 2.4 (3 H, s), 6.7–7.9 (7 H, m), 10.8 (H, d, J = 9 Hz). NMR δ 10.3 (H, d, J = 9 Hz) for *Z* isomer. Anal. ($C_{17}H_{14}O$) C, H.

1,3,6,8-Tetramethyl-9*H*-9-fluorenone (9). Aminobenzophenone **21** (9.4 g, 37 mmol) was dissolved in hot 12 N H_2SO_4 (210 mL). After cooling to 0 °C, the subsequent slurry was treated dropwise with a solution of $NaNO_2$ (3 g) in H_2O (30 mL). The deep yellow suspension was stirred on a steam bath for 2 h before being cooled to 0 °C and filtered. Crystallization of the collected brown solid from MeOH provided **9** (3.8 g, 43%); mp 162–164 °C; NMR δ 2.25 (6 H, s), 2.45 (6 H, s), 6.7 (2 H, s), 7.0 (2 H, s). Anal. ($C_{17}H_{16}O$) H; C: calcd, 86.41; found, 86.86.

(1,3,6,8-Tetramethyl-9*H*-fluoren-9-ylidene)acetaldehyde (10). This compound was prepared by the general aldehyde homologation procedure described in ref 2, starting from **9** (2.4 g, 10 mmol), yield 42% after initial chromatography (silica gel, CH_2Cl_2–hexane; 2:1, R_f 0.40), and crystallization from 2-propanol; mp 112–114 °C; NMR δ 2.3 (6 H, s), 2.4 (6 H, s), 6.65–6.9 (3 H, m), 7.1 (H, br s), 7.2 (H, br s), 10.1 (H, d, J = 7 Hz).

2-Cyano-3-(3,5-dichloro-4′-fluoro[1,1′-biphenyl]-2-yl)-2-propenoic Acid (13). A mixture of **12**[1] (2.7 g, 10 mmol), cyanoacetic acid (940 mg, 11 mmol), pyrolidine (60 μL), acetic acid (200 μL), and toluene (20 mL) was heated at reflux under a Dean–Stark trap for 20 h. The reaction mixture was cooled and evaporated to dryness, and the residue was triturated once with H_2O, dried, and then crystallized twice from toluene–hexane (1:1) to provide **13** (2 g, 60%); mp 203–204 °C; IR (KBr) 2230 (CN) cm^{-1}; NMR (Me_2SO-d_6) δ 7.2–7.6 (4 H, m), 7.62 (H, d, J = 2 Hz), 7.9 (H, d, J = 2 Hz), 8.5 (H, s). Anal. ($C_{16}H_8Cl_2FNO_2$) C, H, N.

2-Cyano-2-(1,3-dichloro-7-fluoro-9*H*-fluoren-9-yl)acetic Acid (14). A mixture of **13** (1.5 g, 4.5 mmol) and anhydrous $AlCl_3$ (1.5 g, 11.2 mmol) in CH_2Cl_2 (75 mL) was stirred under a N_2 atmosphere at 20 °C for 18 h. The deep purple solution was poured into ice-cold 1 N HCl (200 mL). The sticky brown solid was crystallized from *n*-BuCl to yield **14** (900 mg, 60%), mp 191–192.5 °C, as a tan powder: IR (KBr) 2250 (CN, very weak) cm^{-1}; NMR (Me_2SO-d_6) δ 4.7–4.95 (H, m), 5.2–5.4 (H, m), 7.1–7.8 (3 H, m), 8.0–8.3 (2 H, m). Anal. ($C_{16}H_8Cl_2FNO_2$) C, H, N.

(1,3-Dichloro-7-fluoro-9*H*-fluoren-9-yl)acetonitrile (15). A solution of **14** (900 mg, 2.68 mmol) and $Cu(OAc)_2$ (20 mg) in isoquinoline (10 mL) was stirred at 150–160 °C under an atmosphere of N_2 for 0.5 h. The dark reaction mixture was then cooled and distributed between Et_2O (200 mL) and 3 N HCl (100 mL). The organic layer was separated and washed with 3 N HCl (100 mL) and H_2O (2 × 100 mL), dried ($MgSO_4$), filtered, and evaporated to provide **15** (800 mg, 100%); mp 170–173 °C; NMR δ 2.86 (H, dd, J = 18, 7 Hz), 3.36 (H, dd, J = 18, 3 Hz), 4.2 (H, dd, J = 7, 3 Hz), 7.0–7.8 (5 H, m).

(1,3-Dichloro-7-fluoro-9*H*-fluoren-9-yl)acetaldehyde (16). This compound was prepared by Dibal reduction of **15** (800 mg, 2.7 mmol) as described in ref 2: yield 59% as a pale yellow gum [R_f of **16** 0.36 vs. 0.41 for **15** on TLC (silica, $CHCl_3$–hexane (1:1))]; NMR δ 2.8 (H, dd, J = 18, 7 Hz), 3.53 (H, dd, J = 18, 3 Hz), 4.53 (H, dd, J = 9, 3 Hz), 6.95–7.7 (5 H, m), 9.73 (H, s).

2-[(2,4-Dimethylphenyl)carbonimidoyl]-3,5-dimethylbenzenamine (20). A solution of BCl_3 (1 M in CH_2Cl_2, 120 mmol) was slowly added to a cold (−10 °C) solution of **18** (12.1 g, 100 mmol) in dry toluene (150 mL). After the addition was complete, the cooling bath was removed and the mixture was stirred at ambient temperature for 0.75 h. A solution of **19** (14.4 g, 110 mmol) in dry toluene (50 mL) was added, $AlCl_3$ (15 g, 110 mmol) was added, and the cloudy mixture was heated at reflux under a N_2 atmosphere for 20 h after initial distillation of the CH_2Cl_2 and replacement by an equal volume of dry toluene. The reaction mixture was cooled to 20 °C and quenched by the addition of 18

(4) Specific ortho acylation of anilines developed by Sugasawa et al.: Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* **1978**, *100*, 4842.

(5) Chardonnens, L.; Wurmli, A. *Helv. Chim. Acta* **1950**, *33*, 1338.

N H_2SO_4 (250 mL) with vigorous stirring over a 20-min period (the imine was stable in this milieu even at reflux for over 2 h). The organic layer was separated and washed with an additional 250 mL of 18 N H_2SO_4. The acid extracts were combined and back-washed once with Et_2O (500 mL). The acid layer was cooled to 5 °C before the pH was adjusted to 10 by treatment with 20% NaOH. The heavy oil was extracted into Et_2O (2 × 300 mL), and the Et_2O layer was washed with H_2O (2 × 200 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed on silica with CH_2Cl_2–MeOH (40:1). Subsequent crystallization of this product from *n*-BuCl provided **20** (11.3 g, 44%); mp 82–84 °C; NMR δ 1.8 (3 H, s), 2.15 (3 H, s), 2.25 (3 H, s), 2.3 (3 H, s), 6.35 (2 H, s), 6.8–7.25 (3 H, m). Anal. ($C_{17}H_{20}N_2$) C, H, N.

2-Amino-2′,4,4′,6-tetramethylbenzophenone (21). A clear, orange solution of imine **20** (850 mg, 3.37 mmol) in 0.2 N HCl (50 mL) was heated on a steam bath for 10 h. The reaction mixture was cooled and neutralized with NaOH, and the orange gum was extracted into Et_2O. The organic layer was separated and washed with H_2O (2 × 100 mL), dried ($MgSO_4$), filtered, and evaporated to yield **21** (750 mg, 88%) as a heavy oil (R_f of **21** 0.72 vs. 0.29 for **20** on TLC (silica, $CHCl_3$–MeOH (19:1))]; NMR δ 1.8 (3 H, s), 2.2 (3 H, s), 2.3 (3 H, s), 2.45 (3 H, s), 4.45 (2 H, br s), 6.35 (2 H, d, J = 3 Hz), 6.9–7.4 (3 H, m). Anal. ($C_{17}H_{19}NO$) C, H, N.

4-(2,4-Dimethylphenyl)-2,5,7-trimethylquinazoline (22). A clear solution of imine **20** (100 mg, 0.4 mmol) in HOAc (4 mL) and 4 N HCl (6 mL) was heated at reflux for 2 h and then worked up (as for **21**) to provide **22** (80 mg, 72%) as a gum [R_f of **22** 0.57 vs. 0.29 for **20** and 0.72 for **21** on TLC (silica, $CHCl_3$–MeOH (19:1))]; NMR δ 1.95 (3 H, s), 2.0 (3 H, s), 2.37 (3 H, s), 2.47 (3 H, s), 2.85 (3 H, s), 7.1 (4 H, s), 7.65 (H, s); ^{13}C NMR δ 1.95 (CH_3), 21.2 (CH_3), 21.7 (CH_3), 22.7 (CH_3), 26.1 (CH_3 at C-2), 120.1 (C-4a), 126.0 (C-8), 126.5 (C-5′), 128.1 (C-6′), 130.9 (C-6), 131.8 (C-3′), 134.7 (C-2′), 135.9 (C-4′), 138.4 (C-7), 138.8 (C-1′), 143.8 (C-5), 152.9 (C-8a), 162.6 (C-4), 168.6 (C-2).

HMG-CoA Reductase Inhibition Assay. IC_{50} values were determined by plotting percentage inhibition against test compound concentration (four or five levels) and fitting a straight line to the resulting data by using the least-squares method. See part 1 for a full description of protocol.

Acknowledgment. We extend our appreciation to Dr. W. C. Randall and staff for analytical support, to Dr. D. W. Cochran for the ^{13}C NMR spectrum of **22** and helpful discussions on ^1H NMR data, to M. Z. Banker for manuscript preparation, and to Dr. P. S. Anderson for encouragement.

Registry No. **1**, 100430-73-7; **2**, 78444-21-0; **3**, 78444-59-4; **4**, 100484-52-4; **5**, 78444-57-2; **6**, 24061-10-7; **7**, 100430-74-8; **8**, 100430-75-9; **9**, 100430-76-0; **10**, 100430-77-1; **11**, 100430-78-2; **12**, 78444-56-1; **13**, 100430-79-3; **14**, 100448-63-3; **15**, 100430-80-6; **16**, 100430-81-7; **17**, 100430-82-8; **18**, 108-69-0; **19**, 21789-36-6; **20**, 100430-83-9; **21**, 100430-84-0; **22**, 100430-85-1; $Bu_3SnCH{=}CHOEt$, 20420-43-3; $CH_3COCH_2CO_2CH_3$, 105-45-3; 2-$PhC_6H_4CH{=}$CHCHO, 100430-86-2; 6-Ph-2,4-$Cl_2C_6H_2CH{=}CHCHO$, 100430-87-3; 6-(3,4-$Me_2C_6H_3$)-2,4-$Me_2C_6H_2CH{=}CHCHO$, 100448-64-4; 6-(4-FC_6H_4)-2,4-$Cl_2C_6H_2CH{=}CHCHO$, 100430-88-4; 2-(fluoren-9-ylidenyl)acetaldehyde, 4425-71-2; cyanoacetic acid, 372-09-8; HMG-CoA, 9028-35-7.

5,5-Diaryl-2-thiohydantoins and 5,5-Diaryl-N^3-substituted-2-thiohydantoins as Potential Hypolipidemic Agents

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A series of 5,5-diaryl-2-thiohydantoins and 5,5-diaryl-N^3-substituted-2-thiohydantoins related to 5,5-diphenyl-2-thiohydantoin (DPTH) were investigated as potential hypolipidemic agents with the goal of increased potency over DPTH itself. In the 5,5-diaryl class, the best results were obtained by substituting two pyridyl rings for the phenyl rings found in DPTH. The resulting compound, 5,5-bis(2-pyridyl)-2-thiohydantoin, DPYTH (**5**), had slightly better activity than DPTH in lowering liver cholesterol values. Further modifications to DPYTH (**5**) are underway and will be the subject of a future report. In the N^3 nitrogen-substituted series one compound, 5,5-diphenyl-N^3-*n*-butyl-2-thiohydantoin, DPBTH (**7**), showed promise during initial screening, but when analyzed in a dose–response study, its activity was considerably less than that of the parent compound DPTH.

A positive correlation between elevated levels of serum lipids (i.e., cholesterol and triglycerides) and increased incidence of atherosclerosis has been demonstrated.[1] Since coronary heart disease is a major cause of death in Western societies, drugs to lower serum lipid levels have been a major research area in recent years.

Clofibrate [ethyl 2-(*p*-chlorophenoxy)-2-methylpropionate], one of the most widely used hypolipidemic aagents, is relatively ineffective for type IIa hyperlipidemia and is not entirely without undesirable side effects.[2]

In 1972 Elwood et al.[3] reported the activity of 5,5-diphenyl-2-thiohydantoin (DPTH) as a hypolipidemic agent. The results of that study indicated DPTH to be approximately twice as active as clofibrate.

On this basis, a number of derivatives of DPTH were prepared in our laboratory in an effort to improve the effectiveness of this class of compound as hypolipidemic agents. The derivatives were of two types: substitution of one or both phenyl rings at the 4-position and substitution of the nitrogen at the 3-position of the thiohydantoin ring. All of the compounds were tested in the orotic acid assay system as outlined by Elwood et al.,[3] so that a direct comparison could be made with their data.

Concern was expressed about the validity of the orotic acid test system as a measure of hypolipidemic activity since it utilizes the prevention of lipid accumulation in the liver rather than in serum. Examination of Elwood's paper however shows the results of testing a series of compounds in the orotic acid assay that are recognized hypolipidemic agents. Two of these compounds, CPIB and choloxon (D-T_4), are well-known. Since both of these compounds are known to lower serum lipids in humans and also work in the orotic acid assay system, it is inferred that the orotic

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