Hypolipidemic 4,5-Dihydro-4-oxo-5,5-disubstituted-2-furancarboxylic Acids

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Received March 17, 1982

A series of novel 4,5-dihydro-4-oxo-5,5-disubstituted-2-furancarboxylic acids was synthesized and shown to possess potent hypotriglyceridemic activity in normal rats. In contrast to clofibrate, none of the present compounds altered liver weight at any dose. Being more potent than nicotonic acid and clofibrate, 4,5-dihydro-5-methyl-4-oxo-5-phenyl-2-furancarboxylic acid (**5b**, AY-25,712) has been selected for clinical trials.

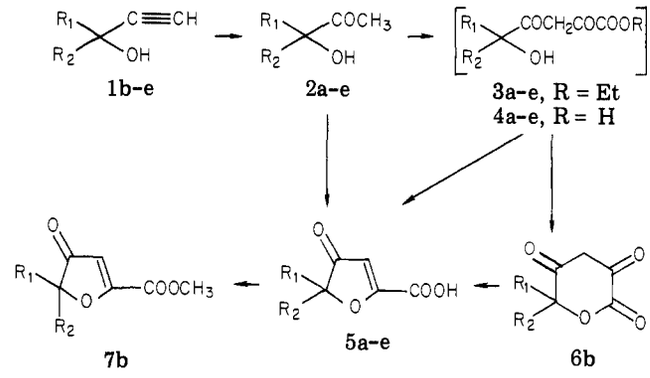
Since dietary changes are often insufficient for the management of hyperlipidemia, lipid-lowering drugs are used as a supplement to dietary control. However, many of the currently available antihyperlipidemic agents are relatively ineffective in certain types of hyperlipoproteinemia and are also associated with side effects. Thus, new and safe antihyperlipidemic compounds are required, agents that would significantly decrease elevated plasma triglycerides, cholesterol, and the LDL/HDL ratio.

The work reported here introduces a new series of potent lipid-lowering 4,5-dihydro-4-oxo-5,5-disubstituted-2-furancarboxylic acids **5a–e**, structurally unrelated to clofibrate and its congeners and, also, markedly different in the pharmacological profile.

Chemistry. Recent investigations in this laboratory have shown[1] that the applicability of the classical Kostanecki reaction can be extended to enolizable β-diketones. In the present study, we have found that a similar condensation of diethyl oxalate with α-hydroxy ketones offers a convenient synthetic route for obtaining 4,5-dihydro-4-oxo-2-furancarboxylic acids with a variety of 5-substituents.

The well-known[2,3] addition of sodium acetylide to ketones R_1–CO–R_2 provided acetylenic carbinols **1b–e** (Scheme I). The subsequent hydration of the triple bond was best accomplished by a modified method of Hennion and Watson,[4] with HgO and H_2SO_4 in aqueous THF. The hydroxy ketones **2b–e** are generally less stable than the carbinols **1b–e** and undergo some decomposition upon distillation. Compound **2e** tends to dehydrate, and its purification sometimes required column chromatography. Condensation of **2a–e** with diethyl oxalate was effected by means of NaH in THF at 55–60 °C. When the reaction mixture is poured into ice–water, the pH of the resultant solution usually does not exceed 8–9, and subsequent acidification results in precipitation of the pyrantrione (exemplified by compound **6b**). Given an option of forming a six- or five-membered ring, the intermediate ester **3b** evidently favors the 6-Exo-Trig closure, i.e., lactonization with the expulsion of the EtO group. When the workup is carried out in a more basic aqueous medium (pH 11) and these conditions are maintained for 24 h before acidification, the resulting carboxylic acids **4a–e** undergo, irreversibly, a 5-Exo-Trig ring closure, and the desired oxofurancarboxylic acids **5a–e** are obtained. Although the esters **3a–e** can be isolated upon acidic workup (methods previously described[1]) and hydrolyzed, and the resulting acids **4a–e** can be cyclized to **5a–e**, it is more convenient to proceed without isolation of these intermediates. Alkaline hydrolysis of **6b**, followed by acid treatment, gave quantitatively **5b**, and, also, a low yield thermal isomerization **6b** → **5b** was observed. Spectral data (see Experimental Section) fully support the structure **6b** and indicate that this compound exists in an enolic form. Acid-catalyzed esterification **5b** → **7b** presented no difficulties.

Scheme I[a]



[a] a, $R_1 = R_2 =$ Me; b, R_1 = Me, $R_2 = C_6H_5$; c, R_1 = Me, R_2 = 4-ClC_6H_4; d, R_1 = *i*-Pr, $R_2 = C_6H_5$; e, R_1 and R_2 = 3′,4′-dihydrospiro[1′(2′*H*)-naphthalene].

Resolution of (±)-**5b** was accomplished by repeated crystallization of its diastereomeric salts with (+)- and (−)-α-methylbenzenemethanamine. To establish optical purity, we coupled the enantiomers (+)-**5b** and (−)-**5b** with (+)-α-methylbenzenemethanamine under DCC catalysis; the resulting amides were separable by GLC, which showed <1% contamination of one by the other.

Biological Results and Discussion

The biological activity of the present compounds was assessed by measuring their effects on serum triglycerides in normal rats, since, in this species, circulating triglyceride levels are more sensitive to clinically effective antihyperlipidemic agents than are cholesterol concentrations.[5] None of the compounds altered food intake or body weight gain.

The data reported in Table I indicate that 4,5-dihydro-4-oxo-5,5-disubstituted-2-furancarboxylic acids are potent hypotriglyceridemic agents. Clearly, compound **5b** (AY-25,712) is the most active analogue of the series, and its methyl ester **7b** also retains marked activity. The isomeric pyrantrione **6b** did not produce comparable effects. Introduction of bulkier, more lipophilic substituents into the 5-position (compounds **5c–e**) attenuated the activity. The potency of **5a** seems to plateau at 0.02 mmol/kg. The chirality at C-5 does not appear to be critical, and (+)-**5b** displayed activities that were essentially of the same magnitude as those of the racemic (±)-**5b**.

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0022-2623/82/1825-1154$01.25/0

Table I. Effect on Serum Triglycerides in Rats[a]

compd	% change from control at various doses, (mmol/kg)/day						
	1.0	0.2	0.1	0.03	0.02	0.01	0.005
5a	−36[b]	−36[c]	−43[b]		−36[c]		
5b	−55[d]	−52[d]	−44[b]	−43[b]	−40[b]	−37[c]	−23
	(218)[e]	(45)	(22)	(6.5)	(4.4)	(2.2)	(1.1)
(+)-**5b**			−38[b]	−29[c]		−39[b]	
(−)-**5b**			−31[c]	−23[c]		−11	
5c		−42[c]			−27		
5d	−53[d]	−31[c]	−2		−10		
5e	−43[b]						
6b		−31[c]	−27		−13		
7b	−53[d]	−40[c]	−40[c]		−34[c]		
clofibrate	−55[c]	−36[b]	−9				

[a] Data obtained from several studies are reported. Rats were treated for 7 consecutive days; each group represents the mean of 8-10 rats. [b] $p < 0.01$. [c] $p < 0.05$. [d] $p < 0.001$. [e] Numbers in parentheses represent the dose of **5b** expressed as milligram per kilogram per day.

Table II. Effect of **5b** (AY-25,712), Clofibrate, and Nicotinic Acid on Serum Triglyceride Levels and Liver Weight in Normal Rat

compd	dose, (mmol/kg)/day[a]	serum triglycerides,[b] mg/dL		liver wt,[b] g	
		control	treated	control	treated
5b	0.05 (11)	104 ± 10.6	58 ± 6.5[c]	8.5 ± 0.29	8.7 ± 0.53
	0.5 (109)	98 ± 10.6	38 ± 3.9[d]	10.2 ± 0.12	10.2 ± 0.20
clofibrate	0.05 (12)	104 ± 10.6	101 ± 15.9	8.5 ± 0.29	8.4 ± 0.28
	0.5 (121)	87 ± 3.5	43 ± 2.7[d]	9.0 ± 0.24	10.7 ± 0.34[c]
nicotinic acid	0.05 (6)	104 ± 10.6	97 ± 10.3	8.5 ± 0.29	8.6 ± 0.35
	0.5 (62)	88 ± 6.5	47 ± 4.9[c]	10.0 ± 0.44	9.1 ± 0.30

[a] Numbers in parentheses represent the dose in milligrams per kilogram per day. [b] Data expressed as mean ± SEM for 8-10 rats per group. [c] Significantly different from control ($p < 0.01$). [d] Significantly different from control ($p < 0.001$).

However (−)-**5b** was 3–4 times less active than (+)-**5b** at the lowest dose tested. In contrast to clofibrate, none of the present compounds altered liver weight at any dose. Thus, these preliminary studies suggested that the pharmacological profile of the acids **5a–e** is different from that of clofibrate and its congeners.

The effects of 1-week treatment with daily oral doses of **5b** (AY-25,712) on serum triglycerides and liver weight were compared with those of clofibrate and nicotinic acid, and the results are presented in Table II. At a dose of 0.05 mmol [11(mg/kg)/day], **5b** significantly lowered serum triglycerides, while similar doses of clofibrate and nicotinic acid had no effect. However, each compound at a dose of 0.5 (mmol/kg)/day produced a hypotriglyceridemia in the normal rat. Clofibrate at 0.5 (mmol/kg)/day significantly elevated liver weight, while nicotonic acid and **5b** had no effect.

Further studies showed that compound **5b** (AY-25,712) produced in rats dose-dependent decreases in circulating LDL-cholesterol. For example, at a dose of 5 (mg/kg)/day for 7 consecutive days, AY-25,712 produced a 31% decrease ($p < 0.01$) in the concentration of serum LDL-cholesterol. The compound also decreased elevated serum lipid concentrations in Triton WR-1339 and streptozotocin-induced hyperlipidemia; the mode of action of AY-25,712 differed from that of clofibrate and resembled that of nicotinic acid.[6] AY-25,712 is not mutagenic in the Ames test and exhibits low acute toxicity (LD_{50} = 3 g/kg po) in rats. Based on these and other studies,[6] compound **5b** (AY-25,712) has been selected for clinical trials.

Experimental Section

Chemistry. The melting points are uncorrected. Analytical results for indicated elements are within ±0.4% of the theoretical values. The IR and UV spectra were obtained on a Perkin-Elmer 225 and Zeiss DMR 21 spectrophotometer, respectively. ^1H NMR spectra were recorded on a Varian CFT-20 instrument at 80 MHz. Chemical shifts are given in parts per million downfield from tetramethylsilane. Mass spectra were determined using an LKB-9000S instrument. Only significant spectral data are reported. Column chromatographies were carried out on silica gel 60 (Merck, mesh 70–230). 3-Hydroxy-3-phenyl-1-butyne (**1b**) and 3-hydroxy-3-methyl-2-butanone (**2a**) were purchased from commercial sources.

Acetylenic Carbinols 1c–e. 3-(4-Chlorophenyl)-3-hydroxy-1-butyne (1c) was synthesized according to Papa et al.:[3] bp 109–110 °C (0.1 mm); yield 48% [lit.[3] bp 120–121 °C (7 mm); yield 56%]. An adaptation of this general procedure[3] allowed preparation of compounds **1d** and **1e**, which were purified by chromatography, eluting with 9:1 (v/v) hexane–Et_2O.

3-Hydroxy-4-methyl-3-phenyl-1-pentyne (1d): yield 77%; NMR ($CDCl_3$) δ 0.85 and 1.07 (doublets, J = 7.5 Hz, 6 H, CH_3), 2.10 (heptuplet, J = 7.5 Hz, 1 H, CH), 2.35 (s, exchangeable, 1 H, OH), 2.66 (s, 1 H, ≡CH), 7.27 (m, 3 H, aromatic CH), 7.55 (m, 2 H, aromatic CH).

1-Ethynyl-1,2,3,4-tetrahydro-1-naphthol (1e):[7] yield 70% conversion 14%); NMR ($CDCl_3$) δ 2.05 (m, 4 H, CH_2), 2.35 (s, exchangeable, 1 H, OH), 2.56 (s, 1 H, ≡CH), 2.79 (t, J = 6.5 Hz, 2 H, benzylic CH_2), 7.10 (m, 3 H, aromatic CH), 7.65 (m, 1 H, H-8).

Hydroxy ketones 2b–e were prepared by a modified method of Hennion.[4] The following example illustrates the general procedure, which eliminates formation of the corresponding methoxy ketones.

3-Hydroxy-3-phenyl-2-butanone (2b).[4] To a refluxing mixture of THF (70 mL), H_2O (5 mL), and concentrated H_2SO_4 (1.5 g) was added red HgO (1 g), and the reflux was continued for 5 min. Then, the inside temperature was adjusted to 55 °C, and **1b** (10 g, 68.5 mmol) in THF (50 mL) was added dropwise. The reaction was slightly exothermic, and the inside temperature was maintained at 55–60 °C. When the addition was complete, the reaction mixture was heated at 60 °C for 2 h. After the mixture was cooled, the resultant slurry was diluted with Et_2O (100 mL) and filtered through Celite, and the filtrate was poured

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into ice–water. The organic layer was separated, and the aqueous phase was reextracted with Et_2O (3 × 70 mL). The combined extracts were dried over $MgSO_4$ and filtered, and the filtrates were evaporated to give 10 g (89%) of **2b**: IR ($CHCl_3$) 3450 and 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.75 (s, 3 H, CH_3), 2.08 (s, 3 H, CH_3CO), 4.50 (s, exchangeable, 1 H, OH), 7.40 (m, 5 H, aromatic CH).

Compounds **2c–e** were prepared in an analogous manner.

3-(4-Chlorophenyl)-3-hydroxy-2-butanone (2c): yield 73%; IR ($CHCl_3$) 3440 and 1712 cm^{-1}; NMR ($CDCl_3$) δ 1.73 (s, 3H, CH_3), 2.07 (s, 3 H, CH_3CO), 4.48 (s, exchangeable, 1 H, OH), 7.40 (narrow m, 4 H, aromatic CH).

3-Hydroxy-4-methyl-3-phenyl-2-pentanone (2d): yield 96%; IR ($CHCl_3$) 3470 and 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (d, J = 7 Hz, 6 H, CH_3), 2.15 (s, 3 H, CH_3CO), 2.79 (heptuplet, J = 7 Hz, 1 H, CH), 4.39 (s, exchangeable, 1 H, OH), 7.20–7.65 (m, 5 H, aromatic CH); MS, m/e (relative intensity, fragment) 192 (0.1, M^+), 175 (1, M – OH), 174 (1, M – H_2O), 149 (100, loss of CH_3CO or C_3H_7).

1-(1,2,3,4-Tetrahydro-1-hydroxy-1-naphthalenyl)ethanone (2e): yield 70%; reaction temperature 50 °C; distillation not recommended; IR ($CHCl_3$) 3450 and 1710 cm^{-1}; NMR ($CDCl_3$) δ 2.01 (m, 4 H, CH_2), 2.09 (s, 3 H, CH_3), 2.83 (m, 2 H, benzylic CH_2), 4.50 (br s, exchangeable, 1 H, OH), 6.75–7.30 (m, 4 H, aromatic CH); MS, m/e (relative intensity, fragment) 190 (absent, M^+), 147 (100, loss of CH_3CO), 129 (15, 147 – H_2O).

General Synthesis of Carboxylic Acids 5a–e. 4,5-Dihydro-5-methyl-4-oxo-5-phenyl-2-furancarboxylic Acid (5b). To a stirred suspension of NaH (10.5 g of a 54% oil dispersion, 0.24 mol) in dry THF (400 mL) was added dropwise a solution of diethyl oxalate (16 g, 0.11 mol) and **2b** (16.4 g, 0.1 mol) in THF (50 mL). The inside temperature was maintained at 55–60 °C. After the addition was complete, the mixture was heated at 60 °C for 18 h. The cold reaction mixture was poured into ice–water, and the resulting solution was adjusted to pH 11 with aqueous NaOH, allowed to stand at room temperature for 24 h, and washed with Et_2O. The aqueous phase was then acidified (pH 1) with 6 N HCl, stirred at ambient temperature for 2 h, and extracted with Et_2O (4 × 250 mL). The combined extracts were dried ($MgSO_4$) and filtered, and the filtrate was slowly concentrated to give 20 g (92%) of **5b**: mp 176 °C; IR (Nujol) 2960–2630, 2540, 1745, 1655 cm^{-1}; UV (MeOH) λ_{max} 281 nm (ε 7960); NMR (CD_3OD) δ 1.75 (s, 3 H, CH_3), 6.21 (s, 1 H, =CH), 7.40 (m, 5 H, aromatic CH); MS, m/e (relative intensity, fragment) 218 (77, M^+), 203 (1, M – CH_3), 200 (3, M – H_2O), *183.5 for 218 → 200, 189 (12, M – CHO), 176 (16, M – CH_2CO), *142 for 218 → 176, 175 (11, M – CH_3CO), 145 (18, 189 – CO_2), 121 (64, Ph $[CH_3]C{=}OH^+$), 105 (63, PhCO), 104 (100, $PhCH{=}CH_2$), 78 (30), 43 (40). Anal. ($C_{12}H_{10}O_4$) C, H.

Similarly, using **2a** and **2c–e** as starting materials, we prepared the following acids.

4,5-Dihydro-5,5-dimethyl-4-oxo-2-furancarboxylic acid (5a): yield 71%; mp 180–181 °C (Et_2O); UV (MeOH) λ_{max} 281 nm (ε 9680); NMR (CD_3OD) δ 1.45 (s, 6 H, CH_3), 6.12 (s, 1 H, =CH); MS, m/e (relative intensity, fragment) 156 (42, M^+), 128 (0.8, M – CO), *105 for 156 → 128, 111 (0.5, M – COOH), 98 (12, loss of acetone), 59 [100, $(CH_3)_2C{=}OH^+$], 43 (42). Anal. ($C_7H_8O_4$) C, H.

5-(4-Chlorophenyl)-4,5-dihydro-5-methyl-4-oxo-2-furancarboxylic acid (5c): yield 72%; mp 169 °C (Et_2O–hexane); MS, m/e (relative intensity, fragment) 254 (12, M + 2), 252 (37, M^+), 155 [100, Cl – C_6H_4 $(CH_3)C{=}OH^+$], 43 (75). Anal. ($C_{12}H_9ClO_4$) C, H.

4,5-Dihydro-5-(1-methylethyl)-4-oxo-5-phenyl-2-furancarboxylic acid (5d): yield 56%; mp 151–153 °C (Et_2O–hexane); NMR ($CDCl_3$) δ 0.77 and 1.01 (doublets, J = 7.5 Hz, 6 H, CH_3), 2.85 (heptuplet, J = 7.5 Hz, 1 H, CH), 6.03 (s, 1 H, =CH), 6.45 (br, 1 H, OH), 7.33 (m, 5 H, aromatic CH). Anal. ($C_{14}H_{14}O_4$) C, H.

3′,4′-Dihydrospiro[furan-5(4*H*),1′(2′*H*)-naphthalene]-4-oxo-2-carboxylic acid (5e): yield 36%; mp 152–154 °C (Et_2O); UV (MeOH) λ_{max} 274 nm (ε 7535), 280 (7500); NMR (CD_3OD) δ 2.07 (m, 4 H, CH_2), 2.85 (m, 2 H, benzylic CH_2), 6.29 (s, 1 H, =CH), 6.75–7.40 (m, 4 H, aromatic CH); MS, m/e (relative intensity, fragment) 244 (70, M^+), 226 (15, M – H_2O), *209.32 for 244 → 226, 215 (5, loss of CHO or Et), 199 (25, M – COOH), 197 (26), 181 (36), 171 (16), 170 (18), 147 (100, naphthalenone + H^+). Anal. ($C_{14}H_{12}O_4$) C, H.

6-Methyl-6-phenyltetrahydropyran-2,3,5-trione (6b). Compound **6b** was prepared from **2b** by the same procedure as for **5b**, except that the cold reaction mixture was poured into ice–water (the resulting pH was 8–9), washed with Et_2O, acidified with 6 N HCl, and extracted with Et_2O (3 × 150 mL). The extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated to afford 18 g (83%) of **6b**: mp 142–144 °C; IR (Nujol) 3130, 1718, 1640 cm^{-1}, UV (MeOH) λ_{max} 268 nm (ε 8830); NMR (CD_3OD) δ 1.89 (s, 3 H, CH_3), 5.92 (s, exchangeable, 1 H, =CH of enol form), 7.35 (s, 5 H, aromatic CH); MS, m/e (relative intensity, fragment) 218 (11, M^+), 190 (14, M – CO), *165.6 for 218 → 190, 121 [100, $Ph(CH_3)C{=}OH^+$], 70 (20, $CH_2COCO^+\cdot$). Anal. ($C_{12}H_{10}O_4$) C, H.

Methyl 4,5-Dihydro-5-methyl-4-oxo-5-phenyl-2-furancarboxylate (7b). A mixture of **5b** (4 g), dry MeOH (250 mL), and concentrated H_2SO_4 (1 mL) was refluxed overnight, concentrated, and diluted with Et_2O (250 mL). The solution was washed quickly with saturated $NaHCO_3$ and H_2O. After drying over $MgSO_4$, it was filtered and concentrated, and **7b** (3.2 g, 75%) crystallized as white clusters: mp 60–62 °C; IR ($CHCl_3$) 1745, 1710 cm^{-1}; UV (MeOH) λ_{max} 283 nm (ε 7800); NMR ($CDCl_3$) δ 1.81 (s, 3 H, CH_3), 3.99 (s, 3 H, OCH_3), 6.25 (s, 1 H, =CH), 7.42 (m, 5 H, aromatic CH). Anal. ($C_{13}H_{12}O_4$) C, H.

Resolution of (±)-5b. To a solution of the racemic **5b** (6.5 g, 29.8 mmol) in *i*-PrOH–Et_2O 1:9 (200 mL) was added a solution of (+)-α-methylbenzenemethanamine (3.63 g, 30 mmol) in Et_2O (50 mL), the resulting solution was chilled to 0 °C, and the crystalline precipitate was collected by filtration. Three crystallizations of this material from MeOH afforded 4.5 g of the (+)-diastereomeric salt: mp 196–198 °C; $[\alpha]^{25}_D$ +110° (c 2, MeOH).

A solution of the salt was stirred with H_2O (100 mL) and Et_2O (100 mL), the aqueous layer was acidified (pH 1) with 6 N HCl, the organic layer was separated, washed with H_2O, dried ($MgSO_4$), and filtered, and the filtrate was evaporated. The residue was crystallized from Et_2O to give 2.7 g (82%) of (+)-**5b**: mp 87–89 °C; $[\alpha]^{25}_D$ +146.4° (c 2, MeOH): IR (Nujol) 3440, 3320, 2540, 2440, 1720, 1669 cm^{-1}. Anal. ($C_{12}H_{10}O_4 \cdot H_2O$) C, H, H_2O.

The (–) enantiomer of **5b** was obtained from the combined filtrates of the initial resolution with (+)-α-methylbenzenemethanamine. These filtrates were evaporated, the residue was partitioned between 0.5 N HCl and Et_2O, the organic layer was separated, and the solvent was removed on a rotavapor. The resulting solids (2.7 g), enriched in the (–)-**5b**, were dissolved in *i*-PrOH–Et_2O, 1:9 (70 mL), and treated with a solution of (–)-α-methylbenzenemethanamine (1.57 g) in Et_2O (30 mL). The crystalline precipitate was collected by filtration and recrystallized thrice from MeOH to give 2.4 g of the (–)-diastereomeric salt: mp 198–199 °C; $[\alpha]^{25}_D$ –108° (c 2, MeOH).

Decomposition of this salt as described above for the (+) enantiomer afforded 1.6 g (49%) of (–)-**5b**: mp 87–89 °C; $[\alpha]^{25}_D$ –144.7°; IR (Nujol) 3440, 3320, 2540, 2440, 1720, 1669 cm^{-1}. Anal. ($C_{12}H_{10}O_4 \cdot H_2O$) C, H, H_2O.

Biological Testing. Male albino Sprague–Dawley rats weighing 130–150 g were kept under observation for 2–3 days and used only if body weight gain during this interval was normal. Animals were maintained on Purina lab chow and were not fasted prior to killing. Compounds were suspended in 2% Tween 80 and administered by gastric intubation daily for 1 week. There were 8–10 rats per group. Animals were decapitated 3 h after the last dose, and blood and liver were removed. Serum triglycerides were measured by the semiautomated method of Kraml and Cosyns.[8] The two-tailed Student's t test was used to determine the significance of difference between group means. For studies comprising more than two groups, one way analysis of variance produced similar statistical differences as did the Student's t test.

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