Adjuvant Arthritis. The method described by Peason[13] was employed. Eight to ten male Sprague–Dawly rats (180–200 g) were used as a group. A suspension of the lyophilized powder of *Mycobacterium butyricum* (Difco) in corn oil was injected into the right hind paw (0.6 mg/0.1 mL per paw) to cause adjuvant arthritis. Test compounds were administered orally 1 h after the adjuvant injection and then followed by daily administration for a period of 18 days. Observation was continued for a period of 28 days.

Acute Toxicity. LD_{50} was determined from the 7-day mortality in male Wistar rats (120–140 g). ED_{50} and LD_{50} values were calculated according to the method of Litchfield and Wilcoxon.[14]

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Registry No. 1, 77674-99-8; 2, 77682-31-6; 2·HCl, 86594-32-3; **3b**, 77675-00-4; **5a**, 77685-58-6; **5a**·HCl, 92760-76-4; **5b**, 77700-96-0; 5b·HCl, 92760-77-5; **5c**, 77683-10-4; **5c**·HCl, 92760-78-6; **5d**, 77683-11-5; **5d**·HCl, 92760-79-7; **5e**, 77683-14-8; **5e**·HCl, 92760-80-0; **5f**, 77683-15-9; **5f**·HCl, 92760-81-1; **6a**, 92669-85-7; **6b**, 77689-68-0; **6c**, 92669-86-8; **6d**, 92669-87-9; **6e**, 92669-88-0; **6f**, 92669-89-1.

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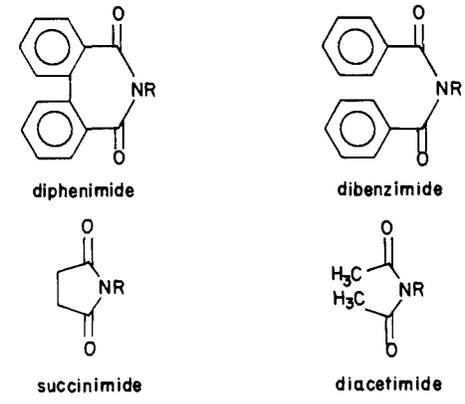
Comparison of the Hypolipidemic Activity of Cyclic vs. Acyclic Imides

P. Josée Voorstad,* J. M. Chapman, G. H. Cocolas, S. D. Wyrick, and I. H. Hall

Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27514. *Received January 23, 1984*

Two series of nitrogen-substituted cyclic and acyclic imides were examined for hypolipidemic activity in mice after dosing for 16 days at a dose of 20 mg/kg per day. The hypolipidemic activity of the unsubstituted, *N*-butyl, *N*-3-oxobutyl, and *N*-2-carboxyethyl derivatives of diacetimide and succinimide were compared as well as the unsubstituted and N-substituted dibenzimide and diphenimide. It was shown that an imide functionality incorporated into a ring was not necessary for hypocholesterolemic activity. Good hypocholesterolemic activity was observed in both series of acyclic and cyclic imides. However, a cyclic imido structure was a necessary requirement for good hypotriglyceridemic activity. A decrease in hypotriglyceridemic activity was noted when comparing the cyclic imides to their respective acyclic congeners.

Chapman and co-workers[1] initially reported the hypolipidemic activity of phthalimide and N-substituted phthalimide in rodents at low doses. Phthalimide, the parent compound, decreased plasma cholesterol and triglyceride levels by 43% and 56%, respectively, in mice after 16 days of dosing at a dose of 20 mg/kg per day.[2] A number of N-substituted phthalimide derivatives including alkyl, methyl ketone, carboxylic acids, and acetate esters of varying chain length were synthesized and tested for hypolipidemic activity in mice. The most significant reduction in serum cholesterol and triglyceride levels were afforded by the administration of *N*-*n*-butylphthalimide, the most active of the alkyl series, *N*-(2-carboxyethyl)-phthalimide, the most active of the acid series, and *N*-(3-oxobutyl)phthalimide, the most active of the methyl ketone derivatives.[1] Further structure–activity relationship studies on the hypolipidemic activity of phthalimide were performed by Chapman[3] and were limited to three areas: (i) substitution on the imide nitrogen of phthalimide, (ii) changes in the structure of phthalimide involving the imide ring system, and (iii) changes in the structure of phthalimide involving the aromatic ring. All compounds structurally related to phthalimide that have been synthesized and examined for hypolipidemic activity to date have possessed an intact imide or lactam ring system. Therefore, a study was conducted in which the importance of the rigid imide ring system for hypolipidemic activity was determined. Two series of acyclic and cyclic imides were synthesized and their hypolipidemic activity in mice compared. The hypolipidemic activities of diphenimide and dibenzimide derivatives were compared as well as those of the succinimide and diacetimide derivatives.



R = H, C_4H_9, $CH_2CH_2C(=O)CH_3$, CH_2CH_2COOH, $CH_2CH_2CO_2C_2H_5$

Experimental Section

Chemistry. Melting points are uncorrected and were determined by using a Mel-Temp capillary melting point apparatus. Thin-layer chromatography was performed with silica gel 60 F-254 TLC plates. Column chromatography was performed with silica gel G-60 (60–200 mesh). ^1H NMR spectra were obtained on either a JEOL FX60 60-MHz nuclear magnetic resonance spectrometer or a Bruker 250 250-MHz nuclear magnetic resonance spectrometer. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, and are correct within ±0.4% of theory. Diacetimide (1) and succinimide (7) were purchased from a commercial source and used as received.

***N*-Butyldiacetimide (2).** By the procedure of Mariella et al.[4] *n*-butylamine (10.0 mL, 0.10 mol) was added dropwise over a period of 15 min to a solution of 0.5 g of anhydrous sodium acetate in acetic anhydride (125 mL, 1.32 mol). The resulting solution was stirred under reflux for 20 h, after which the unreacted acetic anhydride was removed in vacuo. The residue was dissolved in 50 mL of water and the solution was stirred for 45 min and then

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extracted with ether. The ether layer was dried ($MgSO_4$) and the ether removed in vacuo to afford an oil. Distillation of the oil [63–65 °C (0.3 mmHg)] afforded 3.5 g (20%) of *N*-*n*-butyldiacetimide; ^1H NMR ($CDCl_3$) δ (Me_4Si) 3.69 (t, 2 H, NCH_2), 4.20 (s, 6 H, CH_3CO), 0.98–1.76 (m, 7 H, $(CH_2)_2CH_3$). Anal. ($C_8H_{15}NO_2$) C, H, N.

***N*-(3-Oxobutyl)diacetimide (3).** By the procedure of Wichterle et al.,[5] a mixture of 300 mL of 20% HCl and *N*-(3-oxobutyl)phthalimide (40.0 g, 0.18 mol) was stirred under reflux for 12 h. Upon cooling, the precipitate that formed was removed by filtration and the filtrate evaporated in vacuo. By the general procedure of Clark et al.,[6] acetic anhydride (400 mL, 4.20 mol) was added to the residue. The resulting solution was stirred under reflux for 20 h, after which the unreacted acetic anhydride was removed in vacuo. The residue was dissolved in ether and the ether layer dried over anhydrous $MgSO_4$. The ether was removed in vacuo and the residue distilled [85 °C (0.6 mmHg)] to afford 4.4 g (14%) of *N*-(3-oxobutyl)diacetimide as a colorless oil: ^1H NMR ($CDCl_3$) δ (Me_4Si) 3.85 (t, 2 H, NCH_2), 2.75 (t, 2 H, CH_2CO), 2.40 (s, 6 H, CH_3CO), 2.13 (s, 3 H, CH_3CO). Anal. ($C_8H_{13}NO_3$) C, H, N.

***N*-(2-Carboxyethyl)diacetimide (4).** By a modified procedure of Herbst et al.[7] for the synthesis of mono-N-acylated amino acids, β-alanine (40.0 g, 0.45 mol) was dissolved in 150 mL of water and cooled in an ice bath. Acetic anhydride (120 mL, 1.18 mol) was then added in one portion with vigorous stirring. The pH was maintained at pH 5 by the addition of 20% NaOH. The solution was stirred vigorously for an additional 30 min, after which it was acidified to pH 2 by the addition of 10% HCl. The acidic solution was extracted with ethyl acetate, the organic layers were collected and dried ($MgSO_4$), and the ethyl acetate was removed in vacuo to afford crude mono-N-acylated β-alanine as a viscous yellow oil. The crude *N*-acetyl-β-alanine was dissolved in 350 mL of acetic anhydride and the solution stirred under reflux for 7 h. After the reaction was complete, the excess acetic anhydride was removed in vacuo, and the residue dissolved in 5% HCl and extracted with ethyl acetate. The organic layers were collected and dried over anhydrous $MgSO_4$, and the ethyl acetate was removed in vacuo to afford a yellow oil. Column chromatography (ethyl acetate) of the residue afforded a viscous yellow oil which slowly crystallized. The crystals were recrystallized from ethyl acetate to afford 5.4 g (7%) of *N*-(2-carboxyethyl)diacetimide: mp 70–73 °C; ^1H NMR ($CDCl_3$) δ (Me_4Si) 3.98 (t, 2 H, NCH_2), 2.71 (t, 2 H, CH_2CO), 2.46 (s, 6 H, CH_3CO). Anal. ($C_7H_{11}NO_4$) C, H, N.

***N*-(2-Carbethoxyethyl)diacetimide (5).** By the procedure of Kornhauser et al.,[8] acetic anhydride (350 mL, 3.70 mol) was carefully added to β-alanine ethyl ester hydrochloride (40.0 g, 0.25 mol) and the resulting mixture was stirred under reflux for 24 h. The unreacted acetic anhydride was then removed in vacuo and the residue dissolved in ether and extracted with water. The ether layer was dried ($MgSO_4$) and evaporated in vacuo. The resulting oil was distilled twice [83 °C (0.3 mmHg)] to afford 20.0 g (40%) of *N*-(2-carbethoxyethyl)diacetimide: ^1H NMR ($CDCl_3$) δ (Me_4Si) 3.84–4.28 (m, NCH_2, OCH_2), 2.54 (t, 2 H, CH_2CO), 2.32 (s, 6 H, CH_3CO), 1.21 (t, 3 H, CH_2CH_3). Anal. ($C_{19}H_{15}NO_4$) C, H, N.

***N*-Butylsuccinimide (7).** Succinic anhydride (10.0 g, 0.1 mol) was suspended in 80 mL of toluene and butylamine (7.31 g, 0.1 mol) in 20 mL of toluene was slowly added over a 1-h period. The resulting mixture was refluxed for 10 h and 0.1 mL of water was collected by azeotropic distillation. The volatile material was removed in vacuo and the residual oil distilled twice [78–79 °C (0.2 mmHg)] to afford 4.0 g (26%) of *N*-butylsuccinimide. Anal. ($C_8H_{13}NO_2$) C, H.

***N*-(3-Oxobutyl)succinimide (8).** By the general procedure of Irai et al.,[10] succinimide (15.0 g, 0.15 mol) was suspended in 100 mL of ethyl acetate. A catalytic amount of sodium ethoxide was added and the reaction mixture heated to 62 °C. Methyl vinyl ketone (10.9 g, 0.16 mol) was added over a 15-min period and the reaction mixture was then refluxed for 1 h. The volatiles were removed in vacuo to yield a brown oil which was distilled (115–128 °C) to afford N-(3-oxobutyl)succinimide as a colorless oil. Crystallization occurred upon standing and recrystallization from ether afforded 0.8 g (3%) of *N*-(3-oxobutyl)succinimide: mp 50–52 °C; ^1H NMR (acetone-d_6) δ (Me_4Si) 3.82 (t, 2 H, NCH_2), 2.63–2.98 (m, 6 H, CH_2CO), 2.20 (s, 2 H, CH_3).

***N*-(2-Carboxyethyl)succinimide (9).** β-Alanine (8.9 g, 0.1 mol) was suspended in 40 mL of acetone and succinic anhydride (10 g, 0.1 mol) in 60 mL of acetone was slowly added. The reaction mixture was stirred at room temperature for 8 h after which the acetone was removed in vacuo. Acetic anhydride (80 mL, 0.9 mol) was added and the reaction mixture heated at 120 °C for 75 min. The acetic anhydride was removed in vacuo to afford a yellow oil which crystallized upon addition of ether. Recrystallization from ethanol afforded 3.0 g (18%) of *N*-(2-carboxyethyl)succinimide: ^1H NMR ($CDCl_3$/acetone-d_6) δ (Me_4Si) 3.70 (t, 2 H, NCH_2), 2.30–2.80 (m, 6 H, CH_2CO).

***N*-(2-Carbethoxyethyl)succinimide (10).** 3-*N*-Succinimidopropionic acid (2.2 g, 0.013 mol) was suspended in 150 mL of absolute ethanol, and a few drops of concentrated sulfuric acid were added. The mixture was allowed to stand overnight and the volatile material removed in vacuo. The oily residue was distilled [115 °C (0.3 mmHg)] to afford 1.5 g (54%) of *N*-(2-carbethoxyethyl)succinimide as a colorless oil: ^1H NMR ($CDCl_3$) δ (Me_4Si) 4.13 (q, 2 H, OCH_2), 3.82 (t, 2 H, NCH_2), 2.72 (s, 4 H, CH_2CO), 2.61 (t, 2 H, CH_2CO_2), 1.26 (t, 3 H, CH_3). Anal. ($C_9H_{13}NO_4$) C, H, N.

Dibenzimide (11). By the procedure of Titherly,[12] benzoyl chloride (70 mL, 0.5 mol) was added dropwise to a cold (0–5 °C) solution of benzamide (60 g, 0.50 mol) in 300 mL of pyridine. The resulting solution was stirred and kept cold for 8 h, after which the reaction mixture was poured into 1.4 L of water and extracted twice with 400 mL of ether. The ether layer was extracted twice with 300 mL of 10% H_2SO_4 and dried ($MgSO_4$), and upon standing the product crystallized as long needles. The product was collected and recrystallized from ethyl acetate to afford 20.0 g (18%) of dibenzimide: mp 146–147 °C. Anal. ($C_{14}H_{11}NO_2$) C, H, N.

***N*-Butyldibenzimide (12).** Benzoyl chloride (80 mL, 0.69 mol) was added dropwise over a period of 15 min to *n*-butylamine (33 mL, 0.35 mol). The solution was stirred under reflux for 8 h during which time the reaction mixture thickened and darkened in color. The resulting viscous solution was dissolved in 75 mL of hot 2-propanol and cooled to 0 °C. Small quantities of dry ice were added to induce the precipitation of the product. The crystals were collected and recrystallized from 2-propanol to afford 20.0 g (23%) of *N*-butyldibenzimide: mp 72–73 °C; ^1H NMR ($CDCl_3$) δ (Me_4Si) 87.12–7.50 (m, 10 H, aromatic), 4.05 (t, 2 H, NCH_2), 0.80–1.88 (m, 7 H, $(CH_2)_2CH_3$).

***N*-(3-Oxobutyl)dibenzimide (13).** 1-Aminobutan-3-one hydrochloride (5.0 g, 0.04 mol) was dissolved in 60 mL of 20% NaOH and cooled to 5 °C in an ice bath. Benzoyl chloride (5 mL, 0.04 mol) was added dropwise with vigorous stirring. The resulting solution was stirred for an additional 30 min at 5 °C and then overnight at room temperature. The mixture was extracted with methylene chloride, and the organic layers were collected, dried ($MgSO_4$), and evaporated in vacuo to afford 6.6 g (86%) of a viscous yellow oil as the crude *N*-benzoyl-1-aminobutan-3-one. Benzoyl chloride (2.3 mL, 0.02 mol) was added to 20 mL of methylene chloride and cooled to −40 °C. Pyridine (2.6 mL, 0.02 mol) was then added in one portion, followed by the addition of *N*-benzoyl-1-aminobutan-3-one (3.8 g, 0.02 mol) in 15 mL of methylene chloride with vigorous stirring. Stirring was continued for 18 h as the solution was slowly allowed to warm to room temperature, after which it was extracted with 20 mL each of 5% HCl, 5% $NaHCO_3$, and water. The organic layer was collected,

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Table I. Effects of Imides on Serum Cholesterol and Triglyceride Levels in CF_1 Male Mice after Dosing Intraperitoneally for 16 Days at 20 mg/kg per Day

		% inhibn ± SD		
		serum cholesterol		serum triglyceride
no. (N = 6)	compd name	day 9	day 16	day 14
1	diacetimide	4 ± 8	18 ± 4[a]	2 ± 7
2	*N*-butyldiacetimide	11 ± 6	20 ± 8[a]	0 ± 2
3	*N*-(3-oxobutyl)diacetimide	14 ± 8	30 ± 6[a]	20 ± 7[a]
4	*N*-(2-carboxyethyl)diacetimide	20 ± 5[a]	21 ± 4[a]	21 ± 3[a]
5	*N*-(2-carbethoxyethyl)diacetimide	11 ± 11	25 ± 4[a]	11 ± 7
6	succinimide	2 ± 9[b]	27 ± 12[a]	32 ± 7[a]
7	*N*-butylsuccinimide	0 ± 9	15 ± 10	35 ± 4[a]
8	*N*-(3-oxobutyl)succinimide	12 ± 7	10 ± 9	25 ± 11[a]
9	*N*-(2-carboxyethyl)succinimide	32 ± 6[a]	39 ± 13[a]	44 ± 6[a]
10	*N*-(2-carbethoxyethyl)succinimide	11 ± 10	23 ± 8[a]	23 ± 6[a]
11	dibenzimide	14 ± 5[a]	35 ± 7[a]	7 ± 9
12	*N*-butyldibenzimide	23 ± 6[a]	19 ± 6[a]	30 ± 6[a]
13	*N*-(3-oxobutyl)dibenzimide	23 ± 3[a]	26 ± 6[a]	39 ± 8[a]
14	diphenimide	19 ± 7[a]	18 ± 4[a]	19 ± 6[a]
15	*N*-butyldiphenimide	22 ± 7[a]	23 ± 10[a]	48 ± 5[a]
16	1-diphenimidobutan-3-one	23 ± 5[a]	23 ± 7[a]	10 ± 4[b]
17	3-diphenimidopropionic acid	12 ± 11	16 ± 6[b]	25 ± 10[a]
18	phthalimide	37 ± 8[a]	43 ± 7[a]	56 ± 8[a]
19	clofibrate (150 mg/kg)	12 ± 4	13 ± 5[b]	25 ± 5[a]
	control (1% CMC)	0 ± 6[c]	0 ± 5[d]	0 ± 6[e]

[a] $p \leq 0.001$. [b] $p \leq 0.005$. [c] 122 mg % cholesterol. [d] 128 mg % cholesterol. [e] 137 mg % triglyceride.

dried ($MgSO_4$), and evaporated in vacuo to afford 3.1 g of a yellow oil as a mixture of products. Column chromatography (ether) of 1.0 g of the oil afforded 120 mg (5%) of *N*-(3-oxobutyl)dibenzimide: mp 140–142 °C; ^1H NMR ($CDCl_3$) δ (Me_4Si) 7.12–7.50 (m, 10 H, aromatic), 4.31 (t, 2 H, NCH_2), 3.01 (t, 2 H, CH_2CO), 2.22 (s, 3 H, $COCH_3$). Anal. ($C_{18}H_{17}NO_3$) C, H, N.

Diphenimide (14). By the procedure of Underwood et al.,[15] diphenamic acid (25.0 g, 0.10 mol) was added to a solution of 30 mL of glacial acetic acid and 37 mL of acetic anhydride, and the mixture was stirred under reflux for 7.5 h. Upon cooling, the crude product precipitated, which was collected and recrystallized from ethanol to afford 10.0 g (43%) of diphenimide: mp 217 °C. Anal. ($C_{14}H_9NO_2$) C, H, N.

***N*-Butyldiphenimide (15).** By the general procedure of Cole et al.[15] a solution of *n*-butylamine (5 mL, 0.05 mol) in 20 mL of CH_2Cl_2 was added to a solution of diphenic anhydride (10.0 g, 0.05 mol) in 25 mL of CH_2Cl_2. The resulting mixture was stirred under reflux for 2 h after which the volatile material was removed on a steam bath. The residue was dissolved in a solution of 5.0 g of anhydrous sodium sulfate in 50 mL of acetic anhydride and heated on a stream bath for 30 min. Hot water (100 mL) was then added and the resulting solution was extracted with methylene chloride. The organic layer was dried ($MgSO_4$) and the volatile material removed in vacuo. The crude solid residue was recrystallized from methanol to afford 2.2 g (16%) of *N*-*n*-butyldiphenimide: mp 59–60 °C; ^1H NMR ($CDCl_3$) δ (Me_4Si) 7.30 (m, 8 H, aromatic), 4.04 (t, 2 H, NCH_2), 0.32–1.70 (m, 7 H, $(CH_2)_2CH_3$). Anal. ($C_{18}H_{17}NO_2$) C, H, N.

***N*-(3-Oxobutyl)diphenimide (16).** Diphenimide (22.0 g, 0.1 mol) was suspended in 150 mL of ethyl acetate and a catalytic amount of sodium ethoxide was added. The mixture was stirred and heated to 70 °C. Methyl vinyl ketone (13.6 mL, 0.16 mol) was added dropwise over a 10-min period and the final mixture stirred under reflux for 2 h. After the reaction was complete, glacial acetic acid was added until the solution was neutral. The volatile material was removed in vacuo and the residue recrystallized from ethanol to yield 20.5 g (70%) of *N*-(3-oxobutyl)-diphenimide: mp 136–139 °C; ^1H NMR ($CDCl_3$) δ (Me_4Si) 7.30–8.00 (m, 8 H, aromatic), 4.33 (t, 2 H, NCH_2), 2.92 (t, 2 H, CH_2CO), 2.19 (s, 3 H, CH_3CO). Anal. ($C_{18}H_{15}NO_3$) C, H, N.

***N*-(2-Carboxyethyl)diphenimide (17).** A mixture of diphenic anhydride (7.0 g, 0.03 mol), β-alanine (2.7 g, 0.03 mol), and 60 mL of DMF was stirred under reflux for 6 h. The DMF was then removed in vacuo, and the residue was dissolved in 50 mL of acetic anhydride and 10 mL of acetic acid. The solution was stirred under reflux for 2 h, after which the volatile material was removed in vacuo. The residue was recrystallized from 2-propanol to afford 1.5 g (17%) of *N*-(2-carboxyethyl)diphenimide: mp 169–171 °C; ^1H NMR (Me_2SO-d_6) (Me_4Si) 7.50–7.88 (m, 8 H, aromatic), 4.15 (t, 2 H, NCH_2), 2.58 (t, 2 H, CH_2CO). Anal. ($C_{17}H_{13}NO_4$) C, H, N.

Hypolipidemic Screens in Normogenic Mice. Test compounds were suspended in 1% (carboxymethyl)cellulose–water and administered intraperitoneally to CF_1 male mice (~25 g) for 16 days at a dose of 20 mg/kg/per day. On days 9 and 16 blood was collected in nonheparinized microcapillary tubes by tail vein bleeding and the serum obtained by centrifugation for 3 min. The serum cholesterol levels were measured by a modification of the Liebermann–Burchard reaction.[16] Blood was also collected on day 14 in heparinized microcapillary tubes and the serum obtained. Serum triglyceride levels were measured with a commercial kit.[18]

Results and Discussion

A number of the cyclic and acyclic imides demonstrated improved hypolipidemic activity over clofibrate. The opening of the imido ring system of the succinimides and diphenimide series of substituted imides, while retaining an intact imide functional group, had varied effects on hypolipidemic activity in mice (Table I). In some cases the acyclic compound had less hypocholesterolemic activity than the cyclic congener, and in other cases the reverse was true. For example, *N*-(2-carboxyethyl)diacetimide (4) decreased serum cholesterol levels by 21% and its cyclic congener, *N*-(2-carboxyethyl)succinimide (9), decreased serum cholesterol levels by 39% after 16 days of dosing. However, *N*-(3-oxobutyl)diacetimide (3) lowered serum cholesterol levels by 30% whereas its cyclic congener, *N*-(3-oxobutyl)succinimide (8), lowered serum cholesterol levels by only 10%. The differences in hypocholesterolemic activity between the cyclic and acyclic compounds was not related to the group substituted on the nitrogen.

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(17) The synthesis of 3-*N*-dibenzimidopropionic acid was attempted via several routes and was unsuccessful.
(18) Hycel Triglyceride Kit.

In the case of the unsubstituted analogue diacetimide (1) possessed less hypocholesterolemic activity, i.e., 18%, than its cyclic congener, succinimide (6), i.e., 27%; however, dibenzimide (11) possessed greater hypocholesterolemic activity, i.e., 35% than its cyclic congener, diphenimide (14), i.e., 18%.

The ethyl-substituted propionic acids 5 and 10 possessed approximately the same magnitude of hypocholesterolemic activity (25–23%) after 16 days of dosing. It should be noted that the N-substitutions of butyl, butanone, and propionic acid did not dramatically increase the hypocholesterolemic activity of any of the four unsubstituted derivatives. *N*-(3-Oxobutyl)diacetimide (3), *N*-(2-carboxyethyl)succinimide (9), dibenzimide (11), and the butyl (15) and butanone (10) derivatives of diphenimide afforded the best hypocholesterolemic activity of each of the four series.

The opening of the cyclic imido ring system had a more consistent effect on hypotriglyceridemic activity. In most cases, the acyclic compound possessed reduced hypotriglyceridemic activity as compared to the respective cyclic compound.

Unsubstituted succinimide (6) resulted in 32% reduction of triglyceride levels whereas diacetimides only resulted in 2% reduction. The N-substitution of a propionic acid afforded the best hypotriglyceridemic activity of each of the series with 9 affording 44% and 4, 21%. The *N*-(2-carboxyethyl) analogue (9) of succinimide was more effective than unsubstituted succinimide (6) by 12%. The same analogy also holds for the diacetimide series with the propionic acid demonstrating 19% improved activity over diacetimide itself. *N*-(3-Oxobutyl)dibenzimide (13) was the exception to the previous observation in that it demonstrated improved hypotriglyceridemic activity over N-(3-oxobutyl)diphenimide (16) by 29%. Nevertheless, diphenimide (14) and *N*-butyldiphenimide (15) were more active than their respective acyclic derivatives. Compound 15 was the most active in the triglyceride screen of the diphenimide series, affording 48% reduction. The intact imido ring does not appear to be necessary for hypocholesterolemic activity, whereas for hypotriglyceridemic activity, the closed rigid cyclic ring appears to be necessary.

Registry No. 1, 625-77-4; 2, 1563-86-6; 3, 92901-14-9; 4, 92901-15-0; 5, 90609-20-4; 6, 123-56-8; 7, 3470-96-0; 8, 77356-07-1; 9, 5724-76-5; 10, 81416-13-9; 11, 614-28-8; 12, 73491-45-9; 13, 92901-16-1; 14, 3864-08-2; 15, 92901-17-2; 16, 92901-18-3; 17, 92901-19-4; 18, 85-41-6; *n*-butylamine, 109-73-9; acetic anhydride, 108-24-7; *N*-(3-oxobutyl)phthalimide, 3783-77-5; 1-aminobutan-3-one, 23645-04-7; β-alanine, 107-95-9; *N*-acetyl-β-alanine, 3025-95-4; β-alanine ethyl ester hydrochloride, 4244-84-2; succinic anhydride, 108-30-5; methyl vinyl ketone, 78-94-4; benzoyl chloride, 98-88-4; benzamide, 55-21-0; 1-aminobutan-3-one hydrochloride, 92901-20-7; *N*-benzoyl-1-aminobutan-3-one, 71666-56-3; diphenamic acid, 6747-35-9; diphenic anhydride, 6050-13-1.

2-(β-Arylethylamino)- and 4-(β-Arylethylamino)quinazolines as Phosphodiesterase Inhibitors

J. Millen,[†] T. N. Riley,*[‡] I. W. Waters,[§] and M. E. Hamrick[‡]

Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, University, Mississippi 38677.
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The existence of several forms of cAMP phosphodiesterase having differing kinetic characteristics suggests the feasibility of developing tissue-selective inhibitors of this enzyme. This observation is of particular importance in the development of therapeutic agents for the management of reversible obstructive airways disorders. The present report describes the design, synthesis and pharmacological characterization of a series of 6,7-dimethoxyquinazoline derivatives having β-arylethylamine substituents at the 2- or 4-positions. The quinazoline nucleus is intended to confer a high degree of inhibitory activity for phosphodiesterase while the β-aryethylamine moieties are designed to provide selectivity for adrenergically innervated tissue. The target compounds of this study, 6 and 7, were prepared via β-arylethylamine displacement of chloride from an appropriate chloroquinazoline intermediate. The resulting products were evaluated for their ability to relax guinea pig tracheal smooth muscle and as inhibitors of phosphodiesterase.

A major approach to the management of reversible obstructive airway diseases involves the use of agents capable of increasing the intracellular concentration of cyclic adenosine 3′,5′-monophosphate (cyclic AMP). Elevated cyclic AMP levels have been associated with both relaxation of airway smooth muscle[1,2] and inhibition of the release of histamine, leukotrienes, and other mediators of the anaphylactic response.[3,4] A significant research effort has been directed toward the development of β-sympathomimetic agents that stimulate the adenylate cyclase catalyzed synthesis of cyclic AMP.[5,6] Relatively less emphasis, however, has been placed on the development of agents that interfere with the catabolism of cyclic AMP via inhibition of phosphodiesterase. The observation that the enzyme exists in several forms having kinetic characteristics that vary from tissue to tissue[7] supports the feasibility of achieving tissue-selective inhibition of phosphodiesterase. The importance of cyclic nucleotides in modulating cellular function in virtually all mammalian tissues suggests that such selectivity of action is essential in order to obtain therapeutic agents with relatively few side effects.

[†] Ayerst Laboratory Research, Inc., Princeton, NJ.
[‡] Department of Pharmacal Sciences, Auburn University.
[§] Department of Pharmacology, University of Mississippi.

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