Hypolipidemic Activity of Phthalimide Derivatives. 7. Structure–Activity Studies of Indazolone Analogues

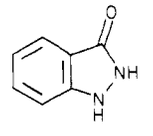
Steven D. Wyrick, P. Joseé Voorstad, George Cocolas, and Iris H. Hall*

Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514. *Received July 25, 1983*

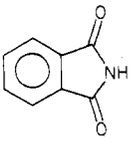
The apparent benefit of limiting serum cholesterol and triglyceride levels either by dietary restriction or drug therapy has prompted work in our laboratories toward development of a suitable antihyperlipidemic agent. We have demonstrated the antihyperlipidemic activity of a series of phthalimide derivatives in rodents to be significantly greater than that of clofibrate at a dose of 20 mg/(kg day), intraperitoneally. Here we report the synthesis and biological evaluation of a series of indazolone derivatives, which are heterocycles that are structurally related to the phthalimides. In general, structure–activity relationships within the phthalimide series may be extended to the indazolones. While indazolone itself is only moderately active, N^1-carbethoxy substitution produced a more active compound. Substitution of the N^2 position with an *n*-butyl group afforded the most active compound, as also seen in the phthalimide series. Aromatic substitution with electron-releasing and -withdrawing groups lessened the antihyperlipidemic activity.

A positive correlation between elevated levels of serum lipids (i.e., cholesterol and triglycerides) and increased incidence of atherosclerosis has previously been demonstrated.[1] Since coronary heart disease is a major cause of death among middle-aged males in Western societies, it appears beneficial to limit serum levels of these lipids by dietary restriction and/or drug therapy.

We have demonstrated the antihyperlipidemic activity of a series of phthalimide analogues[2-4] in rodents to be considerably greater than that of clofibrate, a clinically used antihyperlipidemic agent. Here, we report the effects of molecular modification of indazolone (1), a heterocycle that is structurally related to phthalimide, on antihyperlipidemic activity in mice.



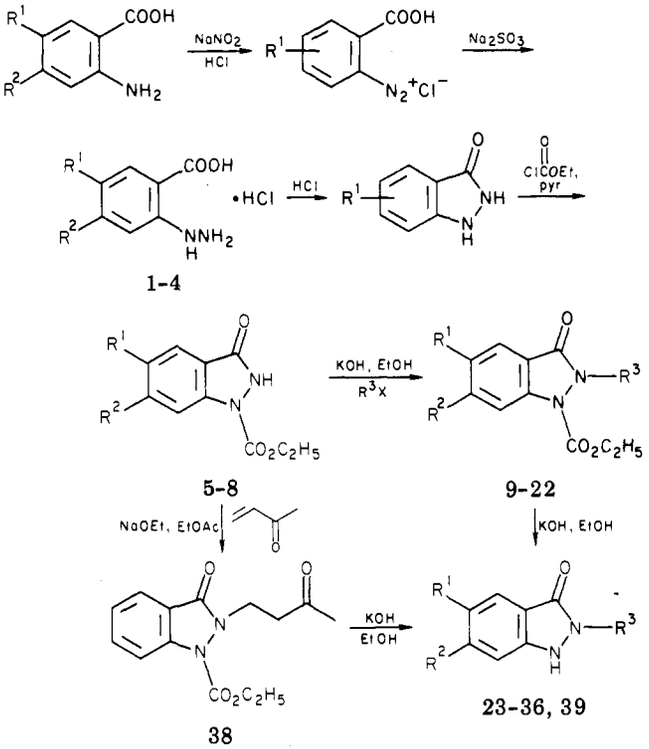
indazolone (1)



phthalimide

Chemistry. Synthetic procedures for formation of the indazolone nucleus and subsequent reactions of this heterocycle have been reviewed by Baiocchi and Corsi.[5] While indazolone (1) itself is commercially available, aryl-substituted indazolones are not. We therefore prepared the aryl-substituted chloro- and methylindazolones (2–4) from the corresponding substituted anthranilic acids by the procedure of Baiocchi and Corsi.[5] This procedure represents a more convenient modification of the earlier procedure of Stephenson[6] for the preparation of indazolone by diazotization of anthranilic acid, followed by reduction to the hydrazine and ring closure (Scheme I). In order to carry out the base-catalyzed alkylation of N^2 of indazolone, the anilino nitrogen (N^1) must first be blocked by carbethoxylation with ethyl chloroformate (5–8). The N^1-carbethoxyindazolones were then N^2-alkylated (9–22) in ethanol in the presence of KOH and the appropriate alkyl bromide or iodide by the procedure of Schmutz[7] or by

Scheme I



Michael addition with methyl vinyl ketone (38) in ethyl acetate.[8] Subsequent decarbethoxylation in ethanolic KOH afforded the N^2-alkylated indazolones (23–26 and 39) (Scheme I).

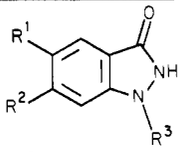
Since substitution of a phenyl ring directly onto the preformed indazolone nucleus is not feasible, N^2-phenylindazolone (37) was prepared from 2-aminobenzophenone according to the procedure of Kametani et al.[9] Diazotization of 2-aminobenzophenone, followed by reduction (Na_2SO_3) to the hydrazine, ring closure, and phenyl migration from C-3 to N^2, afforded the product.

N^1-Carbethoxy-N^2-(2-carboxyethyl)indazolone (40) was prepared by oxidation of the hydroxypropyl precursor (18) with CrO_3 in acetic acid. Attempts to deblock the N^1 position resulted in extensive decomposition of the compound.

(1) Jepson, E. M. *Adv. Drug. Res.* **1974**, *9*, 1.
(2) Chapman, J. M., Jr.; Cocolas, G. H.; Hall, I. H. *J. Med. Chem.* **1979**, *228* 1399.
(3) Chapman, J. M., Jr.; Voorstad, J.; Cocolas, G. H.; Hall, I. H. *J. Med. Chem.* **1983**, *26*, 237.
(4) Hall, I. H.; Williams, W. L., Jr.; Wyrick, S. D.; Voorstad, P. J. *J. Pharm. Sci.*, in press.
(5) Baiocchi, L.; Corsi, G. *Synthesis* **1978**, 633.
(6) Stephenson, E. M. F. In "Organic Syntheses"; Wiley: New York, 1955, Collect. Vol. III, p 475.
(7) Shmutz, J.; Hunziker, F.; Michaelis, *Helv. Chim. Acta* **1964**, *47*, 1986.
(8) Irai, H.; Shinva, S.; Murata, M. *Kogyo Kagaku Zaasshi*, **1959**, *62*, 82.
(9) Kametani, T.; Sota, K.; Shio, M. *J. Heterocycl. Chem.* **1970**, *7*, 815.

0022-2623/84/1827-0768$01.50/0 © 1984 American Chemical Society

Table I. Structural and Physical Characteristics of Aryl-Substituted Indazolones and N^1-Carbethoxyindazolones



compd	R^1	R^2	R^3	yield, %	mp, °C	formula
2	H	Cl	H	67	298–302	$C_7H_5ClN_2O$
3	Cl	H	H	79	281–284	$C_7H_5ClN_2O$
4	CH_3	H	H	84	240–242	$C_8H_8N_2O$
5	H	H	$CO_2C_2H_5$	65	198–201	$C_{10}H_{10}N_2O_3$
6	Cl	H	$CO_2C_2H_5$	76	250–252	$C_{10}H_9ClN_2O_3$
7	H	Cl	$CO_2C_2H_5$	73	215–217	$C_{10}H_9ClN_2O_3$
8	CH_3	H	$CO_2C_2H_5$	82	201–203	$C_{11}H_{12}N_2O_3$

Results and Discussion

Phthalimide, as well as its *N*-alkyl-substituted derivatives, have been shown to possess considerable antihyperlipidemic activity in both normal and atherogenic CF_1 male mice at an optimum dose of 20 mg/(kg day), intraperitoneally (ip).[2] The most potent members in the series are the *N*-*n*-butyl, *N*-butan-3-one, and *N*-propionic acid derivatives. The heterocyclic compound, indazolone (**1**), is a structually related compound in which one of the carbonyls of phthalimide has been replaced by an NH group. Indazolone (**1**) itself is only moderately active as an antihyperlipidemic agent, affording serum cholesterol and triglyceride levels of 80 and 75% of control values, respectively, after 16 days of administration at 20 mg/(kg day), ip. Substitution of N^1 with a carbethoxy group (**5**) produced a more active compound with a 40% reduction of serum cholesterol and 39% reduction of serum triglyceride (Table IV). Within the series of homologous N^2-alkyl derivatives (**23–27**), hypolipidemic activity was optimized by *n*-butyl substitution (**26**) and afforded serum cholesterol and triglyceride levels of 46 and 44% of control values, respectively. A similar trend was evident within the phthalimide series, which required the imide nitrogen to be substituted with a four-carbon chain or a three-carbon and one-oxygen chain for greatest activity.[2] The butan-3-one derivative of indazolone (**39**) also serves to substantiate this trend, affording a reduction of both cholesterol and triglyceride levels of 54%. The trend within the indazolone series deviates from that observed for the phthalimides, however, in that replacement of a carbon atom by an oxygen atom in the *n*-butyl chain to produce **32** diminished antihypercholesteremic activity significantly, but antihypertriglyceridemic activity was affected to a lesser extent relative to **26**. A similar effect on lipid-lowering activities is seen for the hydroxyethyl derivative **31**. Since *n*-butyl substitution at the N^2 position (**26**) afforded one of the two most active derivatives in the series, we decided to examine the effect on activity of aryl substitution of the indazolone nucleus with an electron-releasing group (**30**) and an electron-withdrawing group (**28, 29**) of similar steric and lipophilic value. Results indicate that antihyperlipidemic activity is significantly lessened by this type of substitution. The N^1-carbethoxy-N^2-(2-carboxyethyl) derivative (**40**) showed essentially the same activity as indazolone (**1**) itself and was less active than the N^1-carbethoxyindazolone (**5**), affording serum cholesterol and triglyceride levels of 77 and 70%, respectively.

Within the phthalimide series, nitrogen substitution with a phenyl group or substituted phenyl group afforded a more active compound, i.e., the *N*-(*o*-acetylphenyl) derivative being the most active within the series.[3] Substitution of the N^2 position of indazolone with a phenyl group (**37**) had only a moderate effect on antihypercholesteremic activity (79% of control values) and a moderate effect on antihypertriglyceridemic activity (76% of control values). However, N^2-benzyl substitution (**33**) increased the antihypercholesteremic activity to a slightly greater extent and increased the antihypertriglyceridemic activity substantially. Based on this result, it was decided to substitute the aromatic ring of the benzyl group with *o*-acetyl (**36**), *m*-acetyl (**35**), and *p*-acetyl (**34**) groups as with the phthalimides. As noted with the phthalimides, the *o*-acetyl derivative (**36**) in the N^2-benzylindazolone series was the most active, affording serum cholesterol and triglyceride levels of 60 and 41% of control values, respectively.

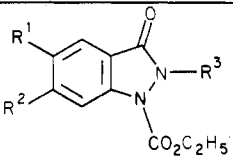
In summary, structure–activity trends observed within the phthalimide series may generally be extended to the indazolones with minor differences in producing hypolipidemic activity in rodents. However, subsequent mechanism of action studies with N^2-*n*-butylindazolone (**26**) demonstrate that this agent was similar to phthalimide in that it lowered available cytoplasmic acetyl-CoA required for cholesterol and fatty acid synthesis, as well as *sn*-glycerol 3-phosphate acyltransferase and phosphatidate phosphohydrolase activities. N^2-*n*-Butylindazolone interfered with the absorption of orally administered cholesterol more significantly than phthalimide, but both agents lowered lipid levels in the tissues and accelerated lipid excretion in the feces via the biliary route.[4]

Experimental Section

All chemicals were used as received from the manufacturer. Melting points were obtained with a Thomas–Hoover melting point apparatus and are uncorrected. Elemental analyses were obtained from MHW Laboratories, Phoenix, AZ, and unless otherwise noted, are correct within 0.4% of theoretical values. Column chromatography was performed on silica gel 60 (70–230 mesh). ^1H NMR spectra were obtained on a JEOL FX-60 Fourier-transform spectrometer. Indazolone (**1**) and phthalimide were obtained from Aldrich Chemical Co.

Aryl-Substituted Indazolones (2–4). General Procedure. The procedure of Baiocchi[5] was used to prepare the aryl-substituted indazolones from the corresponding substituted anthranilic acids. To a suspension of the appropriate anthranilic acid in concentrated HCl/H_2O, 4:1 (~110 mL/0.1 mol of anthranilic acid) was added 1 equiv of $NaNO_2$ in water (15 mL/0.1 mol of $NaNO_2$) at such a rate as to maintain the temperature below 10 °C. After the mixture was stirred with cooling for 30 min, a solution of sodium sulfite (2.7 equiv) in water was added in one portion, and the reaction mixture was stirred for an additional 2 h at room temperature. Concentrated HCl (30 mL/0.1 mol of anthranilic acid) was then added, and the reaction mixture was stirred overnight at room temperature, followed by heating to 80 °C for 6 h. Upon cooling, the pH was adjusted to 5–6 with NaOH, and the resulting precipitate was filtered, washed with water, and dried in vacuo to afford the crude indazolone. Trituration with boiling ethanol afforded the pure product (Table I).

Table II. Structural and Physical Characteristics of N^1-Carbethoxy-N^2-alkylindazolones



compd	R^1	R^2	R^3	^1H NMR ($CDCl_3$, Me_4Si) δ	mp, °C	yield, %	formula
9	H	H	CH_3	7.6 (m, 4 H, Ar H_4), 4.48 (q, 2 H, CH_2), 3.7 (s, 3 H, NCH_3), 1.5 (t, 3 H, CH_3)	oil	85	$C_{11}H_{12}N_2O_3$
10	H	H	C_2H_5	7.6 (m, 4 H, Ar H_4), 4.52 (q, 2 H, OCH_2), 4.35 (q, 2 H, NCH_2), 1.50 (t, 3 H, OCH_2CH_3), 1.24 (t, 3 H, NCH_2CH_3)	oil	44	$C_{12}H_{14}N_2O_3$
11	H	H	n-C_3H_7	7.52 (m, 4 H, Ar H_4), 4.4 (q, 2 H, OCH_2), 1.8 (m, 2 H, NCH_2CH_2) 1.35 (t, 3 H, OCH_2CH_3), 0.7 (7, 3 H, $NCH_2CH_2CH_3$)	oil	28	$C_{13}H_{16}N_2O_3$
12	H	H	n-C_4H_9	7.4 (m, 4 H, Ar H_4), 4.2 (q, 2 H, OCH_2), 3.9 (t, 2 H, NCH_2), 1.81 (m, 4 H, $NCH_2CH_2CH_2$), 1.32 (t, 3 H, OCH_2CH_3), 0.9 (t, 3 H, $NCH_2CH_2CH_2CH_3$)	oil	37	$C_{14}H_{18}N_2O_3$
13	H	H	n-C_5H_{11}	7.55 (m, 4 H, Ar H_4), 3.96 (q, 2 H, OCH_2), 3.7 (t, 2 H, NCH_2), 1.8 [m, 6 H, $NCH_2(CH_2)_3$], 1.3 (t, 3 H, OCH_2CH_3), 0.89 (t, 3 H, $N(CH_2)_4CH_3$)	oil	29	$C_{15}H_{20}N_2O_3$
14	Cl	H	n-C_4H_9	7.78 (m, 3 H, Ar H_3)	oil	9	$C_{14}H_{17}ClN_2O_3$
15	H	Cl	n-C_4H_9	7.52 (m, 3 H, Ar H_3)	oil	15	$C_{14}H_{17}ClN_2O_3$
16	CH_3	H	n-C_4H_9	7.44 (m, 3 H, Ar H_3), 2.44 (s, 3 H, $C_6H_5CH_3$)	oil	39	$C_{15}H_{20}N_2O_3$
17	H	H	CH_2CH_2OH	7.72 (m, 4 H, Ar H_4), 4.58 (q, 2 H, OCH_2), 4.5 (t, 2 H, NCH_2), 4.13 (t, 2 H, CH_2OH), 1.49 (t, 3 H, CH_3)	oil	39	$C_{12}H_{14}N_2O_4$
18	H	H	$(CH_2)_2CH_2OH$	7.65 (m, 4 H, ArH_4), 4.65 (q, 2 H, OCH_2), 4.47 (t, 2 H, NCH_2), 3.81 (t, 2 H, CH_2OH), 2.10 (m, 2 H, NCH_2CH_2), 1.49 (t, 3 H, CH_3)	oil	46	$C_{13}H_{16}N_2O_4$
19	H	H	$C_6H_5CH_2$	7.5 (m, 9 H, Ar H_9), 4.41 (q, 2 H, OCH_2), 5.48 (s, 2 H, $C_6H_5CH_2$), 1.41 (t, 3 H, CH_3)	98–101	64	$C_{17}H_{16}N_2O_3$
20	H	H	p-$CH_3C(=O)C_6H_4CH_2$	7.6 (m, 8 H, Ar H_8), 4.45 (q, 2 H, OCH_2), 5.49 (5, 2 H, $C_6H_4CH_2$), 2.55 (s, 3 H, $COCH_3$), 1.39 (t, 3 H, OCH_2CH_3)	oil	35	$C_{19}H_{18}N_2O_4$
21	H	H	m-$CH_3C(=O)C_6H_4CH_2$	7.62 (m, 8 H, Ar H_8), 4.45 (q, 2H, OCH_2), 5.49 (s, 2H, NCH_2), 2.53 (s, 3H, $COCH_3$), 1.4 (t, 3H, OCH_2CH_3)	semisolid	53	$C_{19}H_{18}N_2O_4$
22	H	H	o-$CH_3C(=O)C_6H_4CH_2$	7.68 (m, 8H, Ar H_8), 4.58 (q, 2H, OCH_2), 5.88 (s, 2H, NCH_2), 2.65 (s, 3H, $COCH_3$), 1.50 (t, 3H, OCH_2CH_3)	semisolid	18	$C_{19}H_{18}N_2O_4$

N^1-Carbethoxyindazolones (5–8).[7] General Procedure. Indazolone or compound **2**, **3**, or **4** was suspended in dry pyridine (250 mL/0.3 mol of indazolone). After the mixture was cooled, ethyl chloroformate (2 equiv) was added dropwise. The reaction mixture was then stirred under reflux for 2 h, concentrated, and poured into water. The precipitate was filtered, washed with water, and air-dried to afford the crude product. This solid was recrystallized from ethyl acetate–methanol (2:1) to afford the pure product (Table I).

N^1-Carbethoxy-N^2-alkylindazolones (9–22).[7] General

Table III. Structural and Physical Characteristics of N^2-Alkylindazolones

compd	R^1	R^2	R^3	^{1}H NMR ($CDCl_3$, Me_4Si) δ	mp, °C	yield, %	formula	anal.
23	H	H	CH_3	7.5 (m, 4 H, Ar H_4), 3.57 (s, 3 H, CH_3)	207–214	57	$C_8H_8N_2O$	C, H, N
24	H	H	C_2H_5	7.35 (m, 4 H, Ar H_4), 3.89 (q, 2 H, NCH_2), 1.34 (t, 3 H, CH_3)	150–152	98	$C_9H_{10}N_2O$	C, H, N
25	H	H	n-C_3H_7	7.4 (m, 4 H, Ar H_4), 3.78 (t, 2 H, NCH_2), 1.7 (m, 2 H, NCH_2CH_2), 0.8 (t, 3 H, CH_3)	89–91	93	$C_{10}H_{12}N_2O$	C, H, N
26	H	H	n-C_4H_9	7.3 (m, 4 H, Ar H_4), 3.67 (t, 2 H, NCH_2), 1.76 [m, 4 H, $NCH_2(CH_2)_2$], 0.73 (t, 3 H, CH_3)	semisolid	100	$C_{11}H_{14}N_2O$	C, H, N
27	H	H	n-C_5H_{11}	7.6 (m, 4 H, Ar H_4), 3.96 (t, 2 H, NCH_2), 1.80 (m, 6 H, $NCH_2(CH_2)_3$], 0.9 (t, 3 H, CH_3)	oil	81	$C_{12}H_{16}N_2O$	H, N; C[a]
28	Cl	H	n-C_4H_9	7.48 (m, 3 H, Ar H_3), 3.87 (t, 2 H, NCH_2), 1.62 [m, 4 H, $NCH_2(CH_2)_2$], 0.89 (t, 3 H, CH_3)	167–171	14	$C_{11}H_{13}ClN_2O$	C, H, N
29	H	Cl	n-C_4H_9	7.60 (m, 3 H, Ar H_3), 3.83 (t, 2 H, NCH_2), 1.58 [m, 4 H, $NCH_2(CH_2)_2$], 0.9 (t, 3 H, CH_3)	149–151	27	$C_{11}H_{13}ClN_2O$	C, H, N
30	CH_3	H	n-C_4H_9	7.54 (m, 3 H, Ar H_3), 3.87 (t, 2 H, NCH_2), 2.38 (s, 3 H, Ar CH_3), 1.51 [m, 4 H, $NCH_2(CH_2)_2$], 0.9 (t, 3 H, CH_2CH_3)	109–111	36	$C_{12}H_{16}N_2O$	C, H, N
31	H	H	CH_2CH_2OH	7.50 (m, 4 H, Ar H_4), 4.51 (t, 2 H, NCH_2), 4.02 (t, 2 H, CH_2OH)	98–100	50	$C_9H_{10}N_2O_2$	C, H, N
32	H	H	$(CH_2)_2CH_2OH$	7.51 (m, 4 H, Ar H_4), 4.55 (t, 2 H, NCH_2), 2.2 (m, 2 H, NCH_2CH_2), 3.82 (t, 2 H, CH_2OH)	88–90	69	$C_{10}H_{12}N_2O_2$	C, H, N
33	H	H	$C_6H_5CH_2$	7.48 (m, 9 H, Ar H_9), 4.99 (s, 2 H, CH_2)	178–180	66	$C_{14}H_{12}N_2O$	C, H, N
34	H	H	p-$CH_3C(=O)C_6H_4CH_2$	7.55 (m, 8 H, Ar H_8), 5.15 (s, 2 H, CH_2)	195–198	63	$C_{16}H_{14}N_2O_2$	C, H, N
35	H	H	m-$CH_3C(=O)C_6H_4CH_2$	7.5 (m, 8 H, Ar H_8), 5.18 (s, 2 H, CH_2), 2.6 (s, 3 H, CH_3)	160–162	75	$C_{16}H_{14}N_2O_2$	C, H, N
36	H	H	o-$CH_3C(=O)C_6H_4CH_2$	7.5 (m, 8 H, Ar H_8), 5.83 (s, 2 H, CH_2), 2.62 (s, 3 H, CH_3)	110–112	40	$C_{16}H_{14}N_2O_2$	C, H, N

[a] C: calc, 70.61; found, 69.10 N: calcd, 13.72; found, 13.41. H: calcd, 7.84; found, 7.86.

Procedure. The appropriate N^1-carbethoxylindazolone (**5–8**) was dissolved in hot ethanol (50 mL/0.04 mol). To this solution was added a solution of KOH (1.25 equiv) in ethanol. A thick suspension of the potassium salt usually formed and was treated with 2.5 equiv of the appropriate alkyl bromide or iodide by dropwise addition. The reaction mixture was then stirred under reflux for 6 h. The volatiles were removed, and the residue was partitioned between ether and water. The ether phase was dried (Na_2SO_4) and evaporated in vacuo to afford a mixture of the O- and N^2-alkylated products. The N^2-alkylated product invariably had the lower R_f value by TLC (SiO_2, CH_2Cl_2–ethyl acetate, 9:1). The mixture was separated by column chromatography (CH_2Cl_2–ethyl acetate, 95:5) to afford the product (Table II).

N^2-Alkylindazolones (23–36). General Procedure. Compounds **9–22** were each hydrolyzed and decarboxylated by stirring under reflux with 4.0 equiv of KOH in ethanol solution (150 mL of ethanol/0.2 mol of KOH) for 4 h. The reaction mixture was cooled to room temperature, 4.0 equiv of glacial acetic acid was added, and the volatiles were removed in vacuo. The residue was partitioned between CH_2Cl_2/H_2O, and the organic phase was dried (Na_2SO_4) and evaporated in vacuo to afford the crude product, which was either column chromatographed (CH_2Cl_2–MeOH, 95:5) or recrystallized from ethyl acetate (Table III).

N^2-Phenylindazolone (37). The procedure of Kametani[9] was used to afford an 11% yield of light tan needles: mp 208–211 °C; ^{1}H NMR ($CDCl_3$; Me_4Si) δ 7.58 (m, 9 H, Ar H_9). Anal. ($C_{13}H_{10}N_{20}$) C, H, N.

N^1-Carbethoxy-N^2-(3-oxobutyl)indazolone (38). The procedure of Irai[8] was used. N^1-Carbethoxyindazolone (5.0 g, 0.024 mol) was suspended in 75 mL of ethyl acetate containing a catalytic amount of NaOEt. The mixture was heated to reflux, followed by the dropwise addition of 1.7 g (0.024 mol) of methyl vinyl ketone. The reaction mixture was stirred under reflux for 1.5 h, during which time a solution was obtained. After the mixture was cooled to room temperature, 2.0 mL of glacial acetic acid was added, and the volatiles were removed in vacuo. The residue was chromatographed on a column of silica gel 60 (CH_2Cl_2–ethyl acetate, 85:15) to afford 4.0 g (60%) of colorless solid: mp 74–76 °C; ^{1}H NMR (δ) ($CDCl_3$; Me_4Si) δ 7.60 (m, 4 H, Ar H_4), 4.44 (q, 2 H, OCH_2), 4.4 (t, 2 H, NCH_2), 2.9 (t, 2 H, CH_2CO), 2.18 (s, 3 H, $COCH_3$), 1.5 (t, 3 H, OCH_2CH_3). Anal. ($C_{14}H_{16}N_2O_4$) C, H, N.

N^2-(3-Oxobutyl)indazolone (39). Compound **38** was treated in a similar manner to **9–22** to afford the product as a colorless solid after repeated column chromatography (CH_2Cl_2; CH_2Cl_2–MeOH, 95:5, 9:1): mp 114–116 °C; ^{1}H NMR ($CDCl_3$; Me_4Si) δ

Table IV. Hypolipidemic Effects of Indazolone Derivatives in CF_1 Male Mice at a Dose of 20 mg/(kg day) ip

	% control		
	serum cholesterol, $\bar{X} \pm SD$		serum triglyceride, $\bar{X} + SD$:
compd ($N = 6$)	day 9	day 16	day 16
1	96 ± 6	80 ± 6[a]	75 ± 6[a]
5	78 ± 5[a]	60 ± 6[a]	61 ± 4[a]
23	92 ± 7	69 ± 5[a]	72 ± 5[a]
24	98 ± 7	71 ± 6[a]	71 ± 6[a]
25	92 ± 6	68 ± 5[a]	77 ± 6[a]
26	92 ± 7	46 ± 4[a]	44 ± 3[a]
27	79 ± 6[a]	73 ± 6[a]	77 ± 6[a]
28	76 ± 6[a]	74 ± 6[a]	83 ± 6[b]
29	98 ± 7	75 ± 5[a]	69 ± 7[a]
30	95 ± 8	97 ± 7	81 ± 6[a]
31	97 ± 7	83 ± 8	63 ± 5[a]
32	96 ± 6	83 ± 7	72 ± 5[a]
33	83 ± 5[a]	72 ± 7[a]	58 ± 6[a]
34	76 ± 6[a]	75 ± 6[a]	50 ± 5[a]
35	86 ± 7[b]	70 ± 5[a]	56 ± 4[a]
36	98 ± 7[a]	60 ± 5[a]	41 ± 3[a]
37	87 ± 6[a]	79 ± 6[a]	76 ± 6[a]
39	78 ± 8[a]	46 ± 5[a]	46 ± 5[a]
40	88 ± 5	77 ± 3	70 ± 7
phthalimide[f]	63 ± 12	57 ± 7	44 ± 8
clofibrate[g]	92 ± 5	87 ± 5	75 ± 6
CM-cellulose[h]	100 ± 5[c]	100 ± 6[d]	100 ± 6[e]

[a] $p \leq 0.001$. [b] $p \leq 0.010$. [c] 118 mg %. [d] 112 mg %. [e] 137 mg/dL. [f] 20 mg/kg. [g] 150 mg/kg. [h] 1%.

7.47 (m, 4 H, Ar H_4), 4.45 (t, 2 H, NCH_2), 3.06 (t, 2 H, Ch_2CO), 2.17 (s, 3 H, CH_3). Anal. ($C_{11}H_{12}N_2O_2$) C, H, N.

N^1-Carbethoxy-N^2-(2-carboxyethyl)indazolone (40). Compound 18 (400 mg, 1.5 mmol) was dissolved in 4 mL of glacial acetic acid and added dropwise to a cooled solution of CrO_3 (608 mg, 6.01 mmol) in 10 mL of glacial acetic acid and 1 mL of water. After stirring overnight at room temperature, the reaction mixture was poured into water and extracted with ether. The ether extracts were dried (Na_2SO_4) and evaporated in vacuo to afford 362 mg of semisolid, which was column chromatographed on silica gel 60 (CH_2Cl_2–MeOH, 9:1) to afford 300 mg (72%) of product as a semisolid: ^1H NMR ($CDCl_3$ Me_4Si) δ 7.60 (m, 4 H, Ar H_4), 4.52 (q, 4 H, OCH_2CH_3, NCH_2), 2.82 (m, 2 H, CH_2COOH), 1.53 (t, 3 H, CH_3).

Assay for Antihyperlipidemic Activity. Compounds **1–5**, **23–37**, **39**, and **40**, as well as clofibrate, were suspended by homogenation in 1% (carboxymethyl)cellulose to deliver 20 mg/kg in 0.2 mL. (Carboxymethyl)cellulose (0.2 mL) was used as a vehicle for the control. Animals were maintained in a group of six, housed in plastic cages on "beta chips", Northeastern Products, and fed Wayne Blox laboratory animal chow ad libitum with water. CF_1 male mice (~25 g) were administered the drugs ip between 9:00 and 11:00 a.m. On days 9 and 16, blood (~1 mL) was obtained by tail bleeding. After centrifugation to obtain serum, 25-μL samples were assayed for total cholesterol by the procedure of Ness et al.[10] Serum triglycerides were assayed by using the commercially available Bio-Dynamics/bmc triglyceride kit on blood collected on the 16th day. By comparison to standards, the milligram percent of cholesterol and milligram per deciliter of triglycerides were calculated. Treated values were expressed (Table IV) as percent of control plus or minus standard deviation. The p values were obtained by using the Student "t" test.

Acknowledgment. This work was supported by National Heart, Lung, and Blood Institute Grant HL25680.

Registry No. 1, 5686-93-1; **2**, 7364-29-6; **3**, 7364-28-5; **4**, 7364-26-3; **5**, 16105-24-1; **6**, 89438-38-0; **7**, 89438-39-1; **8**, 89438-40-4; **9**, 1848-42-6; **10**, 89438-41-5; 11, 89438-42-6; **12**, 89438-43-7; **13**, 89438-44-8; 14, 89438-45-9; **15**, 89438-46-0; **16**, 89438-47-1; **17**, 89438-48-2; **18**, 89438-49-3; **19**, 1848-43-7; **20**, 89438-50-6; **21**, 89438-51-7; **22**, 89438-52-8; **23**, 1848-40-4; **24**, 89438-53-9; **25**, 89438-54-0; **26**, 89438-55-1; **27**, 89438-56-2; **28**, 89438-57-3; **29**, 89438-58-4; **30**, 89438-59-5; **31**, 89438-60-8; **32**, 89438-61-9; **33**, 1848-46-0; **34**, 89438-62-0; **35**, 89438-63-1; **36**, 89438-64-2; **37**, 17049-65-9; **38**, 89438-65-3; **39**, 89438-66-4; **40**, 89438-67-5.

(10) Ness, A. T.; Pastewka, J. V.; Peacock, A. C. *Clin. Chem. Acta* **1964**, *10*, 229.

Synthesis of Previously Inaccessible Quinazolines and 1,4-Benzodiazepines as Potential Anticonvulsants[1]

Aqeel A. Fatmi, Niteen A. Vaidya, W. B. Iturrian, and C. DeWitt Blanton, Jr.*

Departments of Medicinal Chemistry/Pharmacognosy and Pharmacology/Toxicology, College of Pharmacy, University of Georgia, Athens, Georgia 30602. *Received November 3, 1983*

A series of 4,6,7,8-tetrasubstituted 3,4-dihydroquinazolines, quinazolines, quinazolin-2-ones, 1,2,3,4-tetrahydroquinazolin-2-ones, and 5,7,8,9-tetrasubstituted 1,4-benzodiazepines have been synthesized by utilizing the Diels–Alder reaction between furan *o*-amino nitriles and various alkyl or aryl vinyl ketone dienophiles to obtain the anthranilic acid precursors. All of the newly synthesized target compounds were evaluated in mice for anticonvulsant activity. Pro- and anticonvulsant action was quantified by the timed intravenous pentylenetetrazol seizure threshold method. Selected compounds were also evaluated for benzodiazepine receptor binding properties and in vivo antagonist potential. Although the compounds lack potency, the data suggest that previously inaccessible substituted analogues may be useful to segregate the proconvulsant, anticonvulsant, and antagonist actions of benzodiazepines and quinazolines.

Quinazoline and 1,4-benzodiazepine derivatives have been found to be biologically versatile compounds.[2,3] It is probable, but not proven, that these actions involve different mechanisms possessing distinct chemical requirements.[4] Exploiting the Diels–Alder reaction (Scheme I) between furan *o*-amino nitriles and various dienophiles to synthesize novel anthranilic acid derivatives opens avenues for the synthesis of a wide variety of previously inaccessible substituted heterocycles[5] that may be useful

(1) Taken in part from the Ph.D. Dissertation of A. A. Fatmi, University of Georgia, Athens, GA, Aug, 1981.

(2) (a) Amin, A. M.; Mehta, D. R.; Samarth, S. S. *Prog. Drug Res.* 1970, *14*, 218. b) Johne, S. *Ibid.* 1982, *26*, 259.

(3) (a) Garatti, S.; Mussini, E.; Randall, O. L. "The Benzodiazepines"; Raven Press: New York, 1973. (b) Randall, L. O.; Kappel, B. In ref 3a; p 27. (c) Sternbach, L. H. *J. Med. Chem.* 1979, *22*, 1. (d) Fryer, R. I. In "The Benzodiazepines: From Molecular Biology to Clinical Practice"; Costa, E., Ed.; Raven Press: New York, 1983; p 7.

(4) (a) Vida, J. A. "Anticonvulsants"; Academic Press: New York, 1977. (b) Randall, L. O.; Shallek, W.; Sternback, L. H.; Ning, R. Y. In "Psychopharmacological Agents"; Gordon, M., Ed.; Academic Press: New York, 1974; Vol. 3, pp 175–281.

0022-2623/84/1827-0772$01.50/0 © 1984 American Chemical Society