proved not to be suitable for purification. Finally recrystallization from acetonitrile–absolute ethanol gave 1.302 g (71%) of **22** as shiny needles, mp 276.5–278 °C. Anal. ($C_{13}H_{18}BrNO_2$) C, H, Br, N.

5,6-Diacetoxy-*N*-methylcyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline (23). In 27.0 g of trifluoroacetic anhydride and 7.5 g (0.170 mol) of glacial acetic acid, 1.5 g (0.005 mol) of **22** was refluxed overnight. After cooling, the solvent and reactants were removed on the rotary evaporator yielding an oil (2.7 g). Prolonged stirring of the oil under anhydrous ether gave a tan powder (0.92 g) which did not recrystallize from any solvents tried. Therefore, this material was dissolved in ethanol and precipitated by addition of 8% $NaHCO_3$ solution and water. The precipitate was extracted with ether and the ether was evaporated giving an oil which solidified. The solid was recrystallized from 90–120 °C ligroine yielding 176 mg (12%) of **23** as slightly orange prisms, mp 127–128.5 °C. Anal. ($C_{17}H_{21}NO_4$) C, H, N.

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References and Notes

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A New Type of Anticonvulsant: 1-Aryl-3-oxotetrahydroisoquinolines[1]

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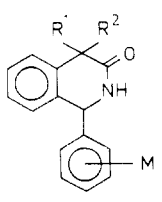
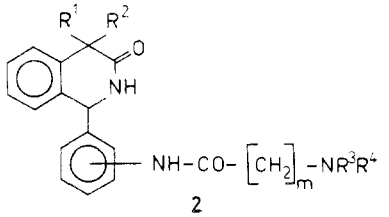
Thirty-two 1-aryl-3-oxotetrahydroisoquinolines have been prepared in which the 2′- or 4′-substituents are (*N*-alkylaminoacyl)amino derivatives. Several derivatives were found to have anticonvulsant properties. A structure–activity relationship study was carried out.

Most known active cyclic anticonvulsants are heterocyclic compounds containing the structural unit of a dilactam (barbiturates, hydantoins, and hexahydropyrimidinediones) or of a diacylamine (oxazolidine-2,4-diones and succinimides). It is, therefore, surprising that 1-aryl-3-oxotetrahydroisoquinolines (**1**), synthesized and tested first in our laboratory,[2,3] and containing only one lactam group, have been found to possess anticonvulsant action.





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1, $R^1 = R^2 = H$, M = H

3, $R^1 = R^2 = H$, M = 4′-NH_2

In the pharmacological tests, the parent substance **1** was found to have a convulsant action in mice, rats, rabbits, and cats, whereas in lower doses an anticonvulsant action was observed protecting mice against electroshock. Later the convulsant action could be eliminated by modifications in the structure; thus, for example, the 1,4′-aminophenyl derivative **3** has a definite anticonvulsant effect.

Introduction of another –CONH– group in the parent compound was tried in order to enhance the efficiency and duration of action. This was realized by acylation of the amino group with alkylaminoacyl groups yielding new compounds with the general formula **2**.

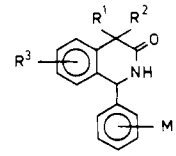
The effects of the following factors on the biological activity of these compounds have been studied: (a) alkyl substitution on the C-4 methylene group; (b) length of the side chain (m = 0–3); and (c) the nature of the alkyl groups R^3 and R^4. Compounds in which the terminal nitrogen in the side chain is part of a five- or six-membered ring have also been prepared.

Chemistry. The 1-[4′-(*N*-alkylaminoacyl)amino]phenyl derivatives (Tables I and II) were obtained by three general methods according to Scheme I. In method A, when m = 1–3, the appropriate 4′-amino derivative was allowed to react with chloroacyl chloride in acetic acid medium in the presence of triethylamine at 50 °C. In the second step, the chloroacetylamino derivatives were condensed with the appropriate amines. In method B, when m = 0 in formula **2**, the 4′-amino derivative was treated with ethyl chloroformate in the first step and then the ethoxycarbonyl derivative formed was used in the preparation of the alkylaminoformyl group, which was formed by aminolysis. Finally, method C was applied in the preparation of derivatives where R^3 and R^4 are hydrogen. In this case, the 4′-amino derivative was first acylated with carbobenzoxyglycine, either by carbobenzoxyglycyl chloride or with the mixed anhydride method; the protective group was then removed from the compound by means of catalytic hydrogenation over Pd/C to yield the 1-(4′-aminoacetylamino)phenyl derivative.

Structure–Activity Relationships. Anticonvulsive Action (Table III). The ED_{50} value could not be determined for five of the compounds examined (**10**, **25**, **31**, **39**, and **41**) even in doses as high as 300 mg/kg; all the other compounds possessed anticonvulsant activity. The protective index was chosen as a measure of activity, which is the ratio of the neurotoxic dose (ED_{50}, rotarod) and the dose inhibiting electroshock (ED_{50}, MES).

On the basis of the protective indices, the active compounds could be divided into three groups: (a) low inhibiting action, $p < 20$ (**3–9**, **21**, **26–29**, **32**, **34–37**, **40**); (b) medium inhibiting action, p = 20–40 (**23**, **24**, **30**, **38**, **42**, and **43**), and (c) strong inhibiting action, $p > 40$ (**22** and **33**).

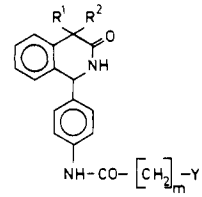
Table I. 1-Aminophenyl-3-oxotetrahydroisoquinolines



No.	R^1	R^2	R^3	M	Yield crystd, %	Crystn solvent[a]	Mp, °C[b]	Formula[c]
3	H	H	H	4′-NH_2·HCl	74	MeOH–Et_2O	249-250	$C_{15}H_{15}ClN_2O$
4	H	H	H	2′-NH_2	79	EtOH	212	$C_{15}H_{14}N_2O$
5	Me	H	H	4′-NH_2	65	EtOH	208	$C_{16}H_{16}N_2O$
6	*i*-Pr	H	H	4′-NH_2	73	T	238-240	$C_{18}H_{20}N_2O$
7	Me	Me	H	4′-NH_2	78	EtOH	204	$C_{17}H_{18}N_2O$
8	Me	Me	7-Me	4′-NH_2	61	EtOH	198-199	$C_{18}H_{20}N_2O$
9	Me	Me	H	2′-NH_2	88	EtOH	185	$C_{17}H_{18}N_2O$
10	H	H	H	3′-NH_2-2′,6′-Cl	64	AcOH	301	$C_{15}H_{12}Cl_2N_2O$

[a] T, toluol. [b] Uncorrected melting points, capillary tube method. [c] All compounds have been analyzed for C, H, and N with results for those elements lying within a ±0.4% limit.

Table II. 1-[4′-(Chloroacetyl)amino]phenyl-, 1-[4′-(*N*-Carbethoxy)amino]phenyl-, 1-[4′-(Benzyloxycarbonylaminoacetyl)amino]phenyl-, and 1-[4′-(Alkylaminoacyl)amino]phenyl-3-oxotetrahydroisoquinolines



No.	R^1	R^2	Y	*m*	Method	Yield crystd, %	Crystn solvent[a]	Mp, °C[b]	Formula[c]
11	H	H	Cl	1	A	82	BuOH	241	$C_{17}H_{15}N_2O_2Cl$
12	Me	H	Cl	1	A	39	BuOH	238	$C_{18}H_{17}N_2O_2Cl$
13	Me	Me	Cl	1	A	65	EtOH	218	$C_{19}H_{19}N_2O_2Cl$
14	*i*-Pr	H	Cl	1	A	78	BuOH	269	$C_{20}H_{21}N_2O_2Cl$
15	H	H	Cl	1	A	76	EtOAc	198	$C_{17}H_{15}N_2O_2Cl$[d]
16	H	H	Cl	3	A	91	AN	238	$C_{19}H_{19}N_2O_2Cl$
17	*i*-Pr	H	Cl	3	A	69	EtOAc	207	$C_{22}H_{25}N_2O_2Cl$
18	H	H	C_2H_5O	0	B	60	EtOH	254-256	$C_{18}H_{18}N_2O_3$
19	Me	Me	NH-Cbz	1	C	52[e]	EtOH	211	$C_{27}H_{27}N_3O_4$
20	Me	Me	NH-Cbz	1	C	22[f]	EtOH	211	$C_{27}H_{27}N_3O_4$
21	H	H	NHMe	1	A	52	EtOH	205	$C_{18}H_{19}N_3O_2$
22	H	H	NHEt	1	A	73	EtOH	188	$C_{19}H_{21}N_3O_2$
23	H	H	NHPr	1	A	72	EtOH	143	$C_{20}H_{23}N_3O_2$
24	H	H	NH-*i*-Pr	1	A	68	EtOH	179	$C_{20}H_{23}N_3O_2$
25	H	H	NEt_2	1	A	80	EtOH	201	$C_{21}H_{25}N_3O_2$[i]
26	H	H	$NHCH_2Ph$[g]	0	B	43	EtOH	172	$C_{23}H_{21}N_3O_2$
27	H	H	NHPr	1	A	43	Ac	132	$C_{20}H_{23}N_3O_2$[i]
28	Me	H	NHPr	1	A	52	Ac-Pe	90	$C_{21}H_{25}N_3O_2$
29	*i*-Pr	H	NHPr	1	A	37	EtOAc	151	$C_{23}H_{29}N_3O_2$
30	Me	Me	NHMe	1	A	65	MeOH	205	$C_{24}H_{27}N_3O_6$[h]
31	Me	Me	NHEt	1	A	75	EtOAc	152	$C_{21}H_{25}N_3O_2$
32	Me	Me	NHPr	1	A	81	Ac-Pe	108	$C_{22}H_{27}N_3O_2$
33	Me	Me	NH-*i*-Pr	1	A	38	EtOH	133	$C_{22}H_{27}N_3O_2$
34	Me	Me	NHBu	1	A	45	EtOH	134	$C_{23}H_{29}N_3O_2$
35	Me	Me	NEt_2	1	A	70	EtOAc	175	$C_{23}H_{29}N_3O_2$
36	Me	Me	NBu_2	1	A	60	EtOAc	142	$C_{27}H_{37}N_3O_2$
37	Me	Me	NH_2	1	C	88	EtOH	166	$C_{23}H_{25}N_3O_6$[h]
38	H	H	C_4H_8NO[j]	1	A	38	MeCH	188	$C_{21}H_{23}N_3O_3$
39	H	H	$C_5H_{10}N$[k]	1	A	40	EtOH	189	$C_{22}H_{25}N_3O_2$
40	H	H	C_4H_8N[l]	3	A	40	EtOH	205	$C_{23}H_{27}N_3O_2$
41	*i*-Pr	H	C_4H_8N[l]	3	A	20	AN	174	$C_{26}H_{33}N_3O_2$
42	Me	Me	C_4H_8NO[j]	1	A	52	EtOH	170	$C_{23}H_{27}N_3O_3$
43	Me	Me	$C_5H_{10}N$[k]	1	A	55	EtOAc	189	$C_{24}H_{29}N_3O_2$

[a] AN, acetonitrile; Ac, acetone; Pe, petroleum ether. [b,c] See footnotes *b* and *c*, respectively, in Table I. [d] 2′ isomer. [e] Mixed anhydride method. [f] Acyl halide method. [g] Ph, phenyl. [h] Maleinate salt. [i] 2′ isomer. [j] C_4H_8NO = 4-morpholino. [k] $C_5H_{10}N$ = 1-piperidine. [l] C_4H_8N = 1-pyrrolidinyl.

Compounds with a nonsubstituted amino group (**3–9**) belong to the group having low inhibiting action. Alkylaminoacyl substitution in the amino group usually enhances the inhibiting action, and the most effective

Table III. Pharmacologic Activity of 1-Phenyl-3-oxotetrahydroisoquinoline Derivatives

No.	MES,[a] ED_{50}, mg/kg,[b] 3 h	PTZ,[c] mg/kg, 3 h	Rot,[d] ED_{50}, mg/kg,[b] 3 h	PI[e]	LD_{50}, mg/kg, 24 h
5,5-Diphenyl-hydantoin	5.2 (3.7-7.3)	26	79.5 (68.5-92.2)	15	>1000
1	105.0 (64.0-172.0)	Inact.	730.0 (563.7-945.4)	7	1060.0 (930.0-1210.0)
3	19.0 (14.0-25.8)	50	~95	5	795.0 (645.0-977.0)
4	140.0 (99.6-196.8)	Inact.	940.0 (653.0-1350.0)	7	>2000
5	26.0 (18.1-37.5)	100	250.0 (199.0-340.0)	10	>2000
6	20.0 (14.5-27.6)	20	358.0 (216.0-594.0)	18	>1600
7	20.0 (14.8-27.0)	100	240.0 (145.5-395.0)	12	>1600
8	70.0 (56.0-87.5)	300	1030.0 (760.0-1400.0)	15	>1600
9	110.0 (58.6-206.3)		>1000	>9	>1000
10	Inact.	Inact.	>1000	Inact.	>1000
21	22.0 (14.0-33.2)	50	270.0 (248.0-295.0)	12	~600
22	10.2 (8.9-11.7)	50	520.0 (449.0-602.0)	51	>1600
23	20.6 (12.1-35.0)	50	490.0 (318.0-754.6)	24	~2000
24	10.5 (7.25-15.2)	100	270.0 (196.0-372.0)	26	>1000
25	Inact.	Inact.	>2000	Inact.	>2000
26	275.0 (167.7-451.0)	Inact.	>2000	>7	>2000
27	180.0 (97.8-331.0)	~300	>2000	>11	>2000
28	22.0 (15.0-32.2)	100	340.0 (240.0-483.0)	15	>1600
29	19.6 (14.0-27.4)	Inact.	~50	~2.5	600-800
30	25.0 (12.8-48.8)	Inact.	~600	~24	>2000
31	Inact.	50	760.0 (590.0-975.0)	Inact.	>2000
32	32.0 (25.4-40.0)	100	435.0 (327.0-580.0)	14	>1600
33	27.0 (20.8-35.2)	100	~1600	~59	>2000
34	23.5 (16.7-35.0)	Inact.	335.0 (186.2-602.0)	14	>2000
35	90.0 (52.0-155.7)	Inact.	~1300	~15	~1600
36	62.0 (44.3-86.8)	Inact.	600.0 (445.0-810.0)	10	>2000
37	32.5 (22.4-47.2)	Inact.	420.0 (280.0-630.0)	13	>1000
38	55.0 (33.7-89.7)	Inact.	>1600	>29	>1600
39	Inact.	300	>2000	Inact.	>2000
40	215.0 (153.0-300.0)	Inact.	>2000	>9	>2000
41	Inact.	Inact.	86.0 (38.6-191.8)	Inact.	>1000
42	78.0 (54.0-110.0)	300	>1600	>20	~2000
43	62.0 (42.5-90.5)	Inact.	>2000	>36	>2000

[a] MES = maximal electroshock seizures. [b] Compounds having no activity in 300 mg/kg were considered as inactive. The values in parentheses are 95% confidence limits. [c] PTZ = antipentylenetetrazole activity; dose increasing the convulsion threshold by at least 50%. [d] Rot = rotarod activity. [e] PI = protective index.

compounds are found in this group (**22**, **33**, and **43**).

In the compounds containing an amino group, the position of the latter in the C-1 phenyl ring has no particular importance; thus **3** and **4** as well as **7** and **9** have nearly the same activity. The situation is different with the *N*-alkylaminoacyl derivatives, where C-2′-substituted derivatives have lower anticonvulsant activity than C-4′-substituted ones (**27** and **23**), or the action is entirely suspended (**25** and **35**). In compounds containing the amino group, introduction of alkyl group(s) at C-4 enhances the activity (**5**–**7**); the effect is the strongest (more than threefold) when an isopropyl group is attached to C-4. However, the relationship is not so unambiguous in the alkylaminoacylamino derivatives, since alkyl substitution at C-4 usually reduces the activity (**22** → **31**, **23** → **28**, **23** → **29**, and **23** → **32**); yet in certain cases (**21** → **30** and **24** → **33**) an increase was observed, or an inactive compound (**39**) became active (**43**).

When examining the effect of the alkyl group in the alkylaminoacyl substituent (**21**–**24**), an increasing action was observed in the series Me, Et, Pr, and *i*-Pr, with a significant peak in the anticonvulsant action when the substituent was the ethyl group. Changes in *m* (*m* = 0, **26**; *m* = 3, **40** and **41**) had no favorable influence on the biological activity of the compounds.

Other effects (on the central nervous system, vegetative system, and circulation) could be elicited only by doses much higher than the anticonvulsant dose.

Experimental Section

Pharmacological Methods. The compounds were studied for possible anticonvulsive activity in mice; they were administered in Tween suspension perorally, 3 h before starting with the experiment.

(a) Maximal Electroshock Seizures (MES). For the MES test, the method of Swinyard[4] was used.

(b) Antipentylenetetrazole Activity (PTZ). For the PTZ test the method of Orloff[5] was used. Compounds were considered as effective when increasing the threshold dose at least by 50% as compared to the saline pretreated controls.

(c) Acute Toxicity (LD_{50}). The dose of the substance necessary to kill one-half of the animals (LD_{50}) was determined 24 h after the administration.

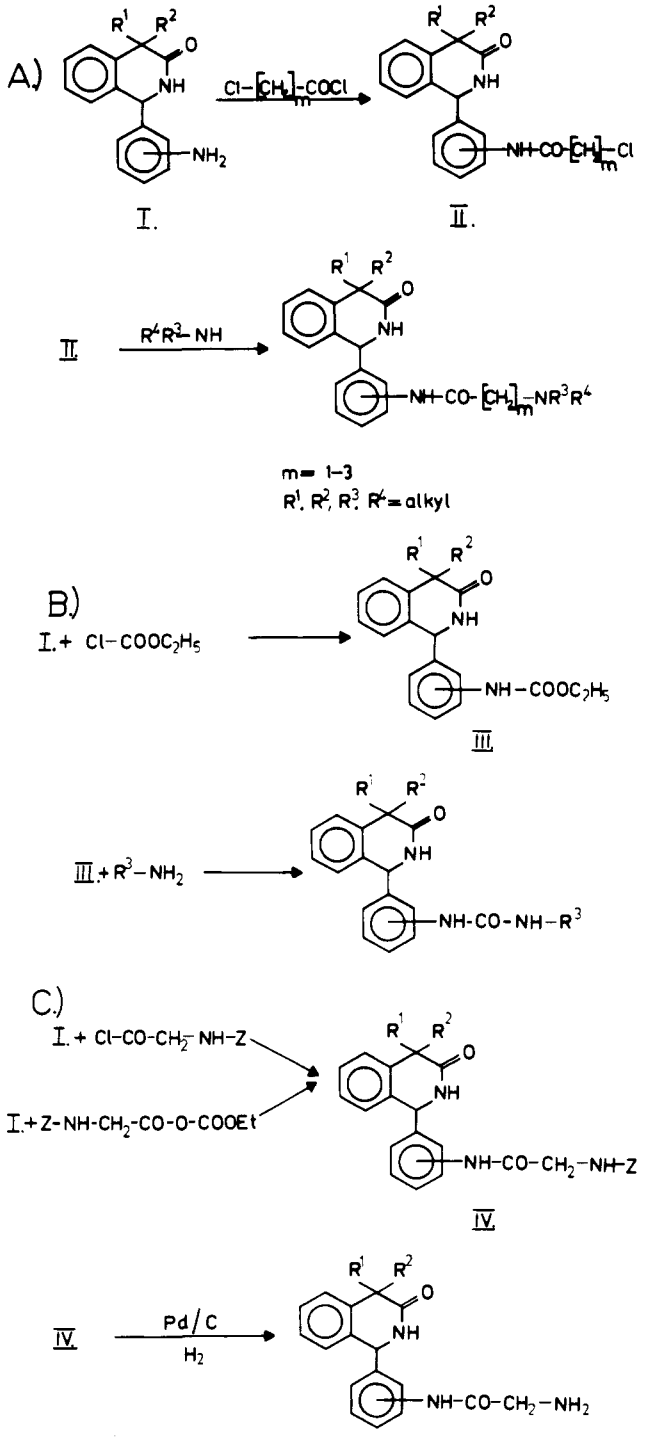
(d) Neurotoxicity. For assessing relative neurotoxicity, a rotarod technique was employed.[6] *Median effective and lethal doses* (ED_{50} and LD_{50}) were determined with 95% confidence limits by the method of Litchfield and Wilcoxon.[7]

Protective Index. In order to compare the efficiency of the compounds exerting a protective action against electroshock, the so-called protective index was applied; this is the ratio of the ED_{50} rotarod and ED_{50} MES values. The higher the ratio, the larger the difference between the dose ensuring protection against electroshock and that causing muscle weakening.

Chemistry. All melting points are uncorrected. Where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements were within 0.4% of the theoretical values.

1-(Nitrophenyl)-3-oxo-1,2,3,4-tetrahydroisoquinolines. The nitro compounds required for the synthesis of the amino derivatives were prepared by the procedures published earlier: 1-(4′-nitrophenyl)-3-oxotetrahydroisoquinoline, 1-(2′-nitrophenyl)-3-oxotetrahydroisoquinoline, 4-isopropyl-1-(4′-nitrophenyl)-3-oxotetrahydroisoquinoline, 4,4-dimethyl-1-(4′-nitrophenyl)-3-oxotetrahydroisoquinoline, and 4,4-dimethyl-1-(2′-nitrophenyl)-3-oxotetrahydroisoquinoline;[2] 4,4,7-trimethyl-1-(4′-nitrophenyl)-3-oxotetrahydroisoquinoline and 1-(2′,6′-dichloro-3′-nitrophenyl)-3-oxotetrahydroisoquinoline.[8]

Scheme I



4-Methyl-1-(4′-nitrophenyl)-3-oxotetrahydroisoquinoline. α-Phenylpropionitrile (35.9 g, 0.27 mol) was added dropwise to polyphosphoric acid (160 g) with stirring. The mixture was heated to 90 °C and stirred further for 45 min; then *p*-nitrobenzaldehyde (20.7 g, 0.14 mol) was added in small portions at such a rate that the temperature increased to 120 °C. The reaction mixture was kept at 120–125 °C for 4 h, cooled to 60 °C, and poured into 1600 mL of water and made alkaline with concentrated ammonium hydroxide, whereupon an oily substance separated. The water was decanted and the product washed with water several times. Finally, it was rubbed with ether to obtain a solid. Crystallization from ethyl acetate and benzene gave a pure and homogeneous product (4.9 g, 12.7%), mp 190–192 °C.

General Method for the Synthesis of 1-Aminophenyl-3-oxotetrahydroisoquinolines. 1-(4′-Aminophenyl)-3-oxotetrahydroisoquinoline Hydrochloride (3). 1-(4′-Nitrophenyl)-3-oxotetrahydroisoquinoline (13.7 g, 0.05 mol) was dissolved in glacial acetic acid (40 mL) and hydrogenated in the presence of 10% Pd/C catalyst (1.5 g) with shaking until the calculated amount of hydrogen had been absorbed (5 h). After filtering off the catalyst, the filtrate was evaporated to dryness in vacuo; the residue was dissolved in water (150 mL), made alkaline with concentrated ammonia, and kept in a refrigerator for 24 h.

The product was collected by filtration, washed with water (75 mL), and dried to give the base (11.6 g, mp 206–208 °C). The base (7.7 g) was dissolved in hot methanol (270 mL), the solution was cooled rapidly, and the pH was adjusted to 2–3 with ether saturated with HCl (60 mL) while cooling in ice–water. Dry ether (70 mL) was then added; the solution was cooled to −20 °C and kept at this temperature for 24 h. The crystalline product was collected by filtration and washed with a mixture of ethanol and ether (2:3) and then with dry ether. The product was dissolved in hot methanol (400 mL), clarified with charcoal, and mixed with dry ether (200 mL) while still slightly warm. The solution was kept at −20 °C overnight, then filtered off, washed with cold absolute ethanol and with dry ether, and dried in a vacuum desiccator. A pure substance (6.1 g, 74.0%), mp 249–250 °C dec, was obtained.

1-(2′,6′-Dichloro-3′-aminophenyl)-3-oxotetrahydroisoquinoline (10). 1-(2′,6′-Dichloro-3′-nitrophenyl)-3-oxotetrahydroisoquinoline (10.1 g, 0.03 mol) was dissolved in glacial acetic acid (150 mL) under stirring and heating. The solution was heated to 90 °C, powdered metallic iron (15 g) was added, and the mixture was stirred at 100–110 °C for 4 h. The solution was filtered while hot, the filtrate was evaporated to dryness in vacuo, and the residue was rubbed with water. The substance which solidified was collected by filtration, thoroughly washed with water and acetone, and dried. The greenish powder was dissolved in hot glacial acetic acid (100 mL) and clarified with charcoal and the product which separated on cooling was recrystallized from acetic acid to obtain **10** (5.8 g, 64%), mp 301 °C.

General Methods for the Synthesis of 1-[4′-(Alkylaminoacyl)amino]phenyl-3-oxotetrahydroisoquinolines. Method A. 1-[4′-(Ethylaminoacetyl)amino]phenyl-3-oxotetrahydroisoquinoline (22). 1-(4′-Aminophenyl)-3-oxotetrahydroisoquinoline (**3**) (32.9 g, 0.138 mol) was dissolved in glacial acetic acid (250 mL) and first triethylamine (15.2 g, 0.15 mol) and then chloroacetyl chloride (16.95 g, 0.15 mol) were slowly added; meanwhile the temperature usually increased to 40–45 °C. The mixture was stirred for 4 h at 50 °C and then poured into ice–water (2000 mL). The precipitate was collected by filtration, washed with water until free from acid, dried, and recrystallized from butanol. The product (35.3 g, 81.5%) was 1-[4′-(chloroacetyl)amino]phenyl-3-oxotetrahydroisoquinoline (**11**), mp 242 °C.

Compound **11** (20.9 g, 0.066 mol) was allowed to react with anhydrous ethylamine (120 mL) in a bomb at 50 °C for 5 h. After cooling, the content of the bomb was poured into ice–water (250 mL); the precipitate was collected by filtration, washed with water, dried, and recrystallized from ethanol to obtain compound **22** (15.6 g, 73.2%), mp 188 °C.

Method B. 1-[4′-(Benzylcarbamoyl)amino]phenyl-3-oxotetrahydroisoquinoline (26). 1-(4′-Aminophenyl)-3-oxotetrahydroisoquinoline (**3**) (14.3 g, 0.06 mol) was dissolved in anhydrous pyridine (160 mL), ethyl chloroformate (6.51 g, 0.06 mol) was added, and the solution was stirred for 2 days until the substance dissolved and some crystalline material started separating. The mixture was poured into 1500 mL of water; the precipitate was collected by filtration, washed with water, dried, and crystallized from ethanol to give 1-[4′-(*N*-carbethoxy)amino]phenyl-3-oxotetrahydroisoquinoline (**18**, 11.2 g, 60%).

Compound **18** (16.3 g, 0.05 mol) was stirred with benzylamine (60 mL) at 180 °C for 2 h; the precipitate was collected by filtration after cooling, washed with 2 N HCl and then with water, dried, and crystallized from ethanol to obtain **26** (8.3 g, 42.6%), mp 171–172 °C.

Method C. 1-[4′-(Benzyloxycarbonylaminoacetyl)amino]phenyl-4,4-dimethyl-3-oxotetrahydroisoquinoline (19). (**a**) 1-(4′-Aminophenyl)-4,4-dimethyl-3-oxotetrahydroisoquinoline (**7**, 3.72 g, 0.014 mol) was dissolved in anhydrous dimethylformamide (30 mL) and mixed with triethylamine (1.47 g, 0.0145 mol), with cooling to 0 °C and stirring. A solution of freshly

prepared α-benzyloxycarbonylaminoacetyl chloride[9] (3.3 g, 0.0145 mol) in dry dimethylformamide (20 mL) cooled to 0 °C was added dropwise, and the reaction mixture was stirred between 0 and −5 °C for 2 h and then at room temperature for further 5 h. Pouring into water (500 mL) caused an oily substance to separate, which was extracted with chloroform, and the extract was washed with water and dried over Na_2SO_4, and the solvent evaporated. The residual oil was rubbed with water; the solid was collected by filtration, washed with water, and dried. After recrystallization from ethanol, 1-[4′-(benzyloxycarbonylaminoacetyl)amino]-phenyl-4,4-dimethyl-3-oxotetrahydroisoquinoline (**19**, 1.4 g, 21.4%) was obtained, mp 211 °C.

(**b**) α-Benzyloxycarbonylaminoacetic acid (5.23 g, 0.025 mol) was dissolved in anhydrous dimethylformamide (50 mL) and triethylamine (2.63 g, 0.025 mol) was added to the solution with stirring. The solution was cooled to −10 °C and ethyl chloroformate (2.71 g, 0.025 mol) was added, by drops. The temperature rose to 0 °C, and triethylamine hydrochloride separated as a white precipitate. After 20 min, a solution of **7** (6.65 g, 0.025 mol), in anhydrous dimethylformamide (50 mL) and cooled to 0 °C, was added; the mixture was then stirred at 0 °C for 3 h and at 25 °C for 5 h. It was poured into water (1000 mL); the precipitate was collected by filtration, washed with water, and dried. Recrystallization from ethanol gave **19** (6.0 g, 52.5%).

1-[4′-(Aminoacetyl)amino]phenyl-4,4-dimethyl-3-oxotetrahydroisoquinoline Maleate Salt (37). A solution of **19** (4.8 g, 0.01 mol) in DMF (150 mL) was mixed with glacial acetic acid (0.72 g, 0.012 mol), and the solution was hydrogenated in the presence of 10% Pd/C catalyst (2 g) under stirring, until the evolution of CO_2 had ceased. The solution was filtered, the filtrate evaporated to dryness, and the residue dissolved in water and made alkaline. An oil separated which soon solidified; this was filtered off, washed with water until neutral reaction, and dried in vacuo. The crude product was converted into the maleate salt according to the well-known procedure. On recrystallization from ethanol, 1.8 g (57.5%) of the product was obtained, mp 165–167 °C.

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Hypolipidemic Analogues of Ethyl 4-Benzyloxybenzoate

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A series of compounds related to ethyl 4-benzyloxybenzoate was synthesized and evaluated for potential hypolipidemic activity in rats. Structure–activity relationships are discussed in terms of cholesterol-lowering activity together with effects on body weight gain and liver lipids. A number of the compounds inhibited cholesterol and free fatty acid biosynthesis from [1-^{14}C]acetate in rat liver slices in vitro. Ethyl 4-benzyloxybenzoate, ethyl-4-benzyloxybenzoic acid, ethyl 4-*p*-bromobenzyloxybenzoate, and ethyl 4-*o*-methoxybenzyloxyphenyl acetate exhibited the most favorable spectrum of activity.

Considerable numbers of aryloxy- and alkyloxy-substituted aryl- and alkylcarboxylic acids have been reported to possess hypolipidemic properties,[1] but only Clofibrate, ethyl 2-(*p*-chlorophenoxy)-2-methylpropionate, has achieved any degree of success in general medicine. However, the low potency of Clofibrate with respect to low-density lipoprotein levels in man has stimulated great efforts to develop a more effective agent. We wish to report here the evaluation of a series of compounds derived from ethyl 4-benzyloxybenzoate (**1**) as potential hypolipidemic agents. Structural modifications and substitutions were carried out on **1** yielding a series of analogues which produced various effects on serum cholesterol and triglyceride levels in rats. While this work was in progress the hypolipidemic activity of alkoxybenzoic acids was reported in the patent literature[2] and more recently further results were published in this Journal.[3]

Chemistry. The compounds were prepared by standard methods as detailed in Table I and in the Experimental Section.

Biological Evaluation. Compounds were examined for hypolipidemic activity as detailed in the Experimental Section.

In addition to serum cholesterol and triglyceride, certain other parameters were measured. Body weight gain during the experimental period gave an indication of gross toxicity (if any) of the compounds. Liver weight as a percentage of body weight (i.e., relative liver weight) was routinely measured. This determination is important since many drugs affect this organ in different ways. Goldberg[4] has proposed that, in certain instances, liver enlargement should be considered as an adaptive functional response of the liver to an increased work load. Clofibrate shows this effect in rats after a short period (17–36 days), but the liver eventually returns to normal.[5] Certain compounds, for example, *N*-γ-phenylpropyl-*N*-benzyloxyacetamide (W1372),[6] that exhibit hypolipidemic activity cause a concomitant increase in liver lipid. This effect can be considered undesirable and was therefore monitored in our evaluation.

Further evaluation of compounds which exhibited pronounced hypolipidemic properties together with