Synthesis and Hypotensive Activity of Some Cyclopentano-1,2,3,4-tetrahydroisoquinolines

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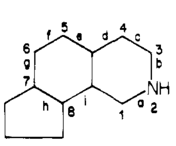
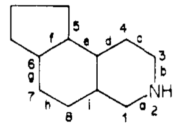
A series of derivatives of the novel cyclopentano[*f*]- and [*h*]-1,2,3,4-tetrahydroisoquinolines has been synthesized and screened for hypotensive properties in the unanesthetized DCA hypertensive rat and for acute toxicity in the mouse. Substitutions were made in the parent structures at both the heteroatom and the 5 and 6, and 7 and 8 positions. Bulky lipophilic substitutions on the heteroatom yielded compounds producing moderate depressions in blood pressure over extended periods of time. One member of the series produced a significant hypertensive response. Some heart stimulant properties (unaccompanied by effects on blood pressure) were observed with some compounds. In general, the compounds were relatively toxic. The introduction of the bulky lipophilic groupings on the heterocyclic nitrogen appeared to be associated with a reduction in toxicity.

Our longtime interest in isoquinolines possessing cardiovascular activities[1,2] has included the synthesis of several tetrahydroisoquinolines which were shown to possess significant hypotensive properties.[2] More recently our laboratories have been involved in the synthesis of some novel tricyclic structures based on the tetrahydroisoquinoline nucleus.[3,4] The series of compounds reported here was designed to investigate the cyclopentano-1,2,3,4-tetrahydroisoquinoline nucleus as a potential hypotensive building block. Derivatives of the isomeric cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline (I) and cyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline (II) ring systems have been prepared. The synthesis of the precursor molecules for the current study, 5,6-dimethoxycyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline (**13**) and 7,8-dimethoxycyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline (**1**), has been previously reported.[3]



I

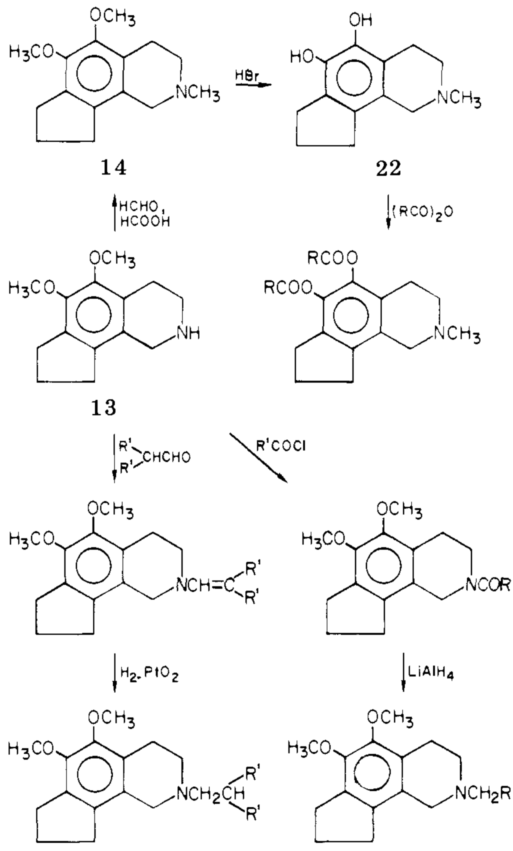


II

Our earlier studies on hypotensive reduced isoquinolines indicated that the incorporation of lipophilic substituents at the isoquinoline nitrogen led to decreased toxicity without loss of the hypotensive response[2] and that various ester groupings in the nonheterocyclic ring yielded compounds with interesting blood pressure lowering properties.[5] With these facts in mind, structural modifications of the precursor molecules **1** and **13** included the incorporation of various oxygenated groupings at positions 5 and 6 in **13** and 7 and 8 in **1** and the substitution of lipophilic moieties on the heteroatom in the form of substituted alkyl, alkanoyl, aralkanoyl, and aralkyl groupings. The compounds were screened for hypotensive activity in deoxycorticosterone acetate (DCA) treated hypertensive rats and the mean systolic blood pressure and heart rate were recorded for periods up to 24 h. Structure–activity relationships of these novel tricyclic series of compounds are discussed.

Chemistry. The series of derivatives were prepared from the precursors **1** and **13**, in general, by the pathway shown in Scheme I using precursor **13** as an example. The compounds synthesized, their purification solvents, and other physical data are shown in Tables I and II. In many instances purification of the product was achieved via the hydrobromide or other salt.

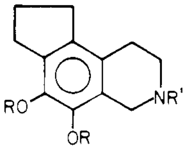
Scheme I



R = alkyl grouping
R' = aryl, aralkyl, or alkyl grouping

Pharmacological Evaluation. Acute toxicity determinations were performed in female Swiss-Webster mice weighing 15–24 g. Compounds were administered either in aqueous solution or as suspensions in 1% tragacanth or propylene glycol by the intraperitoneal route to groups of animals consisting of three or more mice per group. Approximate LD$_{50}$ values were estimated from the results

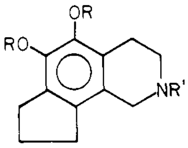
Table I. Physical Data of Substituted Cyclopentano[*f*]-1,2,3,4-tetrahydroisoquinolines



Compd no.	R	R′	Mp, °C	Formula	Analyses	Purificn solvent	Yield, %
1[a]	CH_3	H					
2·HBr	CH_3	CH_3	228.5-230	$C_{15}H_{22}BrNO_2$	C, H, Br, N	EtOH-EtOAc	41
3·HBr	CH_3	$CH_2CH(CH_3)C_2H_5$	139.5-142	$C_{19}H_{30}BrNO_2$	C, H, Br, N	EtOAc	16
4	CH_3	$CO[3,4\text{-}(CH_3O)_2]C_6H_3$	Oil	$C_{23}H_{27}NO_5$	C, H, N	Column chromatography	29
5·HCl	CH_3	$CH_2[3,4\text{-}(CH_3O)_2]C_6H_3$	222.5-224	$C_{23}H_{20}ClNO_4$	C, H, N, Cl	Acetonitrile	57
6	CH_3	$COCH_2[3,4\text{-}(CH_3O)_2]C_6H_3$	Oil	$C_{24}H_{29}NO_5$	C, H, N	Column chromatography	39
7·HBr	CH_3	$CH_2CH_2[3,4\text{-}(CH_3O)_2]C_6H_3$	234-236	$C_{24}H_{32}BrNO_4$	C, H, N, Br	Acetonitrile	71
8	CH_3	$CH_2CH(C_6H_5)_2$	100-102	$C_{28}H_{31}NO_2$	C, H, N	MeOH	28
9	CH_3	$COCH_2CH(C_6H_5)_2$	Oil	$C_{29}H_{31}NO_3$	C, H, N	Column chromatography	27
10	CH_3	$CH_2CH_2CH(C_6H_5)_2$	105-106.5	$C_{29}H_{33}NO_2$	C, H, N	MeOH	54
11·HBr	H	CH_3	242-244	$C_{13}H_{18}BrNO_2$	C, H, N, Br	Acetonitrile	43
12·F_3C-CO_2H	$COCH_3$	CH_3	169.5-172	$C_{19}H_{22}F_3NO_6$	C, H, N, F	EtOH	42

[a] See ref 3.

Table II. Physical Data of Substituted Cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinolines



Compd no.	R	R′	Mp, °C	Formula	Analyses	Purificn solvent	Yield, %
13[a]	CH_3	H					
14·HBr	CH_3	CH_3	133-136	$C_{15}H_{22}BrNO_2$	C, H, Br, N	EtOH-ether	45
15·HBr	CH_3	$CH_2CH(CH_3)C_2H_5$	156.5-158	$C_{19}H_{30}BrNO_2$	C, H, Br, N	EtOAc	47
16	CH_3	$CO[3,4\text{-}(CH_3O)_2]C_6H_3$	106-108	$C_{23}H_{27}NO_5$	C, H, N	Petr ether[b]	39
17·HBr	CH_3	$CH_2[3,4\text{-}(CH_3O)_2]C_6H_3$	226-228.5	$C_{23}H_{30}BrNO_4$	C, H, Br, N	Ether	68
18	CH_3	$COCH_2[3,4\text{-}(CH_3O)_2]C_6H_3$	101-102	$C_{24}H_{29}NO_5$	C, H, N	Column chromatography	44
19·HBr	CH_3	$CH_2CH_2[3,4\text{-}(CH_3O)_2]C_6H_3$	235-236	$C_{24}H_{32}BrNO_4$	C, H, Br, N	Acetonitrile	22
20	CH_3	$COCH(C_6H_5)_2$	Oil	$C_{28}H_{29}NO_3$	C, H, N	Column chromatography	59
21	CH_3	$CH_2CH(C_6H_5)_2$	116.5-118	$C_{28}H_{31}NO_2$	C, H, N	EtOH	30
22·HBr	H	CH_3	276.5-278	$C_{13}H_{18}BrNO_2$	C, H, Br, N	Acetonitrile-EtOH	45
23	CH_3CO	CH_3	127-128.5	$C_{17}H_{21}NO_4$	C, H, N	Petr ether[b]	12

[a] See ref 3. [b] Bp 90-120 °C.

obtained by administering two or more dose levels of each compound, usually spaced 0.3 logarithmic intervals or less, to these groups of mice. Animals were observed for up to 72 h following injection of the compounds, but the toxicity values reported in Table III represent the outcome 24 h after administration of the compounds.

The induction of hypertension in male Charles River rats and the indirect measurement of blood pressure and heart rate were conducted in the manner previously described;[2] therefore, only a summary is included here for completeness and the benefit of the reader. Control systolic blood pressure and heart rates were determined in a group of usually six DCA hypertensive rats on each test day. A compound for evaluation was administered by intraperitoneal injection either in aqueous or propylene glycol solution or as a suspension in 1% tragacanth. Blood pressure and heart rate were redetermined at 1-, 2-, 4-, and 24-h intervals following injection. Mean values of the group for these parameters at a particular measurement period were calculated and then the mean difference from control, along with its associated standard error, was calculated for each time period. The statistical significance of the changes produced by a compound was tested by an analysis of variance and the Newman-Keuls a posteriori test[6] when *F* was significant. A probability level of 0.05 or less was accepted as a significant change.

Results and Discussion

The pharmacologic data obtained is shown in Table III. In four instances (18-20 and 23) insufficient material was available for meaningful pharmacological studies and in these cases only toxicity data were obtained. In general, the compounds did not possess hypotensive activities in a widespread manner throughout the series. However, notable activities were observed for significant periods of time with specific examples and in some cases at relatively small doses.

The compounds were generally quite toxic, the parent compounds 13 and 14 demonstrating the greatest toxicity. The presence of highly lipophilic substituents on the

Table III. Acute Toxicity and Cardiovascular Activity of Some Substituted Cyclopentano-1,2,3,4-tetrahydroisoquinolines. Cardiovascular Activity in DCA Hypertensive Rat

Compd no.	Vehicle of admin	Controls^a	Dose^b	% change in pressure and heart rate from control ± SE^c				ALD$_{50}$^{d}
				1 h	2 h	4 h	24 h	
1	W^e	201 ± 8.7	10	−3.1 ± 2.2	−3.4 ± 2.8	−14.2 ± 1.9^h	−7.2 ± 3.7	79-89
		(356 ± 21)		(+5.8 ± 6.4)	(+8.1 ± 5.6)	(+3.9 ± 7.9)	(−9.1 ± 4.1)	
		184 ± 5.9	20	−3.9 ± 1.1	−4.0 ± 2.7	−3.9 ± 3.4	−0.2 ± 2.0	
		(336 ± 14)		(+10.2 ± 5.0)	(+16.9 ± 6.4)	(+11.0 ± 6.2)	(+7.4 ± 4.9)	
		188 ± 7.8	50	No detectable pulse	No detectable pulse	No detectable pulse	−16.8 ± 8.7	
		(336 ± 15)					(+10.0 ± 8.6)	
2	W	185 ± 4.4	20	+6.3 ± 2.1	+5.5 ± 1.5	−4.2 ± 3.3	−2.9 ± 1.1	100–150
		(356 ± 14)		(+3.5 ± 1.6)	(+9.2 ± 2.1)	(+8.5 ± 5.1)	(+1.5 ± 4.6)	
		208 ± 12.1	50	−3.0 ± 5.5	−2.9 ± 2.4	−6.3 ± 2.2	−4.6 ± 2.7	
		(383 ± 10)		(−8.7 ± 2.3)	(−4.4 ± 3.2)	(+1.6 ± 3.9)	(−3.8 ± 5.0)	
3	W	181 ± 2.4	10	−12.2 ± 2.2^h	−1.9 ± 2.3	+0.7 ± 1.4	−2.6 ± 2.1	100–200
		(371 ± 13)		(+3.6 ± 3.9)	(−4.2 ± 2.9)	(−4.3 ± 5.7)	(−2.4 ± 3.6)	
		173 ± 5.6	20	−13.1 ± 2.7^h	−8.1 ± 2.8^h	−7.0 ± 1.2^h	−1.6 ± 0.8	
		(376 ± 12)		(+7.8 ± 5.8)	(+7.3 ± 4.5)	(+3.4 ± 2.0)	(−5.5 ± 2.2)	
4	P^f	176 ± 3.6	20	−4.0 ± 3.3	−1.4 ± 3.5	−3.1 ± 3.2	+5.6 ± 3.8	150–200
		(350 ± 9)		(+3.8 ± 2.1)	(+8.9 ± 3.8)	(+2.2 ± 3.8)	(+5.7 ± 1.3)	
5	T^g	170 ± 5.5	50	−8.8 ± 2.9	−4.2 ± 3.2	−0.7 ± 1.7	+0.9 ± 3.3	141–159
		(384 ± 11)		(+13.0 ± 5.3)	(+9.0 ± 4.2)	(+10.2 ± 6.0)	(−1.3 ± 3.4)	
6	P	186 ± 8.1	20	+5.4 ± 1.8^h	−3.9 ± 2.0	−6.3 ± 1.1^h	−3.1 ± 1.1	160–180
		(341 ± 10)		(+1.9 ± 1.3)	(+1.8 ± 2.7)	(+1.3 ± 4.4)	(−6.7 ± 2.2)	
7	T	170 ± 4.5	50	−26.0 ± 4.3^h	−11.3 ± 2.2^h	−6.6 ± 4.2	−2.8 ± 2.8	125–140
		(344 ± 11)		(+22.0 ± 2.2^h)	(+17.6 ± 4.1^h)	(+5.4 ± 3.6)	(+2.4 ± 2.4)	
8	T	182 ± 4.2	20	+1.4 ± 1.8	+1.1 ± 3.3	−2.9 ± 1.4	−3.0 ± 2.7	>1000
		(387 ± 13)		(+7.4 ± 1.9^h)	(+10.7 ± 2.7^h)	(+0.8 ± 1.1)	(−5.0 ± 2.0^h)	
		182 ± 6.9	100	−10.7 ± 2.6^h	−12.7 ± 2.9^h	−11.2 ± 3.0^h	−3.6 ± 0.3	
		(378 ± 6)		(+8.7 ± 2.5^h)	(+2.4 ± 2.5)	(+2.4 ± 3.4)	(−2.4 ± 2.5)	
9	P	214 ± 5.7	20	−4.4 ± 0.9	−6.9 ± 3.0	−5.0 ± 1.9	−2.1 ± 1.3	100–180
		(364 ± 13)		(+16.8 ± 5.3^h)	(+15.8 ± 7.2^h)	(+2.4 ± 3.6)	(−1.8 ± 2.7)	
10	T	183 ± 7.2	100	−3.5 ± 3.5	−7.9 ± 2.7^h	−6.7 ± 1.6^h	−7.0 ± 1.8^h	1000
		(394 ± 22)		(+4.0 ± 2.0)	(+4.6 ± 1.8)	(+0.8 ± 1.5)	(+0.6 ± 2.1)	
11	W	195 ± 6.1	50	−1.1 ± 2.5	+2.6 ± 2.7	+3.0 ± 3.6	−3.6 ± 3.9	150–200
		(343 ± 15)		(+8.2 ± 4.1)	(+4.8 ± 3.6)	(+4.1 ± 4.2)	(+3.0 ± 4.1)	
12	W	185 ± 7.0	50	−13.1 ± 4.1^h	+5.2 ± 3.8	−0.6 ± 3.9	−5.1 ± 2.8	200
		(318 ± 8)		(+14.6 ± 4.7^h)	(+7.3 ± 2.6)	(+2.6 ± 2.7)	(+0.3 ± 5.4)	
13	W	194 ± 5.0	5	−9.5 ± 3.8	−3.0 ± 2.7	−6.5 ± 3.3	+1.8 ± 3.7	25
		(349 ± 19)		(−5.2 ± 2.2)	(−1.4 ± 2.1)	(−8.5 ± 3.7^h)	(−12.2 ± 3.4^h)	
		199 ± 7.8	10	No detectable pulse	−13.2 ± 2.0^h	+2.4 ± 1.6	+1.0 ± 3.3	
		(320 ± 8)			(+4.7 ± 4.2)	(+9.0 ± 3.7)	(−2.6 ± 2.5)	
14	W	187 ± 10.4	4	+13.0 ± 4.6^h	+12.2 ± 1.5^h	−2.6 ± 2.9	+19.7 ± 5.0^h	10
		(342 ± 9)		(+13.2 ± 4.4^h)	(+11.2 ± 3.0^h)	(−0.4 ± 4.8)	(+1.8 ± 1.7)	
15	W	172 ± 5.1	25	−17.2 ± 4.8^h	−12.6 ± 4.4^h	−6.7 ± 5.3	+1.3 ± 5.0	178–200
		(345 ± 16)		(+13.7 ± 5.7)	(+11.8 ± 5.4)	(+5.0 ± 5.4)	(−0.3 ± 2.4)	

16	T	177 ± 4.5	100	−12.1 ± 2.2[h]	−8.8 ± 2.2[h]	−3.4 ± 1.5	−6.0 ± 2.0[h]	>1000
		(388 ± 15)		(+0.2 ± 1.6)	(+3.4 ± 1.8)	(−1.2 ± 1.7)	(−6.5 ± 2.4[h])	
17	T	184 ± 4.8	50	−8.4 ± 2.8	−2.4 ± 4.1	−1.0 ± 1.1	+3.3 ± 2.4	200–250
		(366 ± 14)		(+0.4 ± 2.2)	(+0.4 ± 1.8)	(+1.0 ± 1.9)	(−9.1 ± 4.6)	
18	T							500–1000
19	T							100–200
20	P							200–500
21	T	182 ± 5.4	100	−5.0 ± 2.4	−3.4 ± 3.3	−2.0 ± 3.0	+4.0 ± 5.2	>1000
		(356 ± 12)		(+18.5 ± 6.5[h])	(+25.4 ± 5.5[h])	(+8.6 ± 5.0)	(−0.5 ± 4.9)	
22	W	188 ± 5.6	50	−9.1 ± 2.7	−3.5 ± 2.4	−5.7 ± 3.3	−3.7 ± 3.0	160–200
		(380 ± 16)		(−1.9 ± 6.2)	(+5.1 ± 4.7)	(+4.6 ± 4.3)	(−8.6 ± 3.6)	
23	T							150–250
α-Me-Dopa	T	205 ± 9.0	50	−31.0 ± 3.6[h]	−50.0 ± 4.2[h]	−47.7 ± 5.6[h]	−16.5 ± 5.3[h]	
		(378 ± 21.5)		(106.2 ± 26.0[h])	(+104.1 ± 27.8[h])	(+31.0 ± 39.2)	(−19.3 ± 12.4)	

[a] Mean systolic blood pressure (mmHg) ± SE. Numbers in parentheses represent mean heart rate (beats/min) ± SE. [b] Expressed as milligrams of base. [c] Numbers in parentheses represent percent change in heart rate from control ± SE. [d] Approximate LD$_{50}$ expressed as milligrams of base per kilogram. [e] W = distilled water. [f] P = propylene glycol 400. [g] T = 1% tragacanth. [h] Significant change at 0.05 probability level.

heterocyclic nitrogen yielded the least toxic compounds (e.g., **8**, **10**, **16**, and **21**). Surprising differences in toxicity were noted between comparable members of the isomeric series (e.g., **4** vs. **16**; **6** vs. **18**; **2** vs. **14**); in general, however, marked toxicity was not associated with either series of compounds although the most toxic compounds of the entire group (**13** and **14**) belonged to the cyclopentano-[*h*]tetrahydroisoquinoline group.

From the limited data obtained compounds **3**, **7**, and **16** clearly emerged as possessing some potential as lead compounds, producing statistically significant depressions in blood pressure for periods up to 24 h at doses ranging from 20 to 100 mg/kg. Concomitant decreases in blood pressure and significant increases in heart rate occurred in some instances (e.g., compound **7**). Consideration of the data will be made under two general groups—those compounds corresponding with Table I and those with Table II.

A. Compounds 1–12. At the doses screened, only four compounds were found to produce significant decreases in blood pressure. Interestingly, of these compounds **3**, **7**, and **8** produced their greatest effect at the earlier time periods while the more lipophilic compound **10** appeared to have a longer period of onset of action and remained effective over the remainder of the 24-h recorded period. It was interesting that with compounds **3** and **10**, no increases in heart rate accompanied the blood pressure decrease, while with compound **7** substantial and with **8** moderate increases in heart rate were apparent. In this series, the most lipophilic compounds (**8** and **10**) were the most active and the least toxic. The anticipated improvement of hypotensive activity by incorporation of ester moieties did not materialize; compound **12** produced a significant blood pressure drop at only the first hour reading.

B. Compounds 13–23. This series of isomeric ring structures to those discussed above (**1–12**) produced only a few compounds (**15** and **16**) with significant blood pressure lowering responses. The hypotensive effects were unaccompanied by an increase in heart rate. The activity of compound **14** was somewhat surprising in that it produced marked increases in blood pressure at a dose of 4 mg/kg which contrasted with its structural isomer **2** which was devoid of blood pressure effects and was much less toxic than **14**. This pressor response was noteworthy in that it was the only member of the entire series exhibiting such a response and was one of only a few pressor compounds which have appeared in our extensive work on reduced isoquinolines.[1,2,5] The pressor response of **14** was accompanied by substantial increases in heart rate. In several cases (e.g., **9** and **21**), increases in heart rate occurred in the absence of blood pressure effects suggesting some heart stimulant properties of this class of compounds. The increases in heart rate observed with those compounds producing decreases in blood pressure may be a result of both the compensatory heart rate increase due to blood pressure lowering as well as the direct heart stimulant properties. The largest blood pressure depressor effects in this group were observed with compound **15**; however, the effect was not sustained beyond the 2-h period. Interestingly, the depressor response of this compound was not accompanied by significant changes in heart rate.

Experimental Section

All melting points were determined using a Swissco melting point apparatus and are uncorrected. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn., and Chemalytics, Inc., Tempe, Ariz. Where analyses are indicated, values within ±0.4% of the theoretical values were considered acceptable. Infrared (IR) spectra were recorded on a Beckman Model IR-33 grating spectrophotometer. Nuclear magnetic resonance (NMR) spectra were determined on a Hitachi Perkin-Elmer Model R-24 spectrometer and deuterium exchanges were routinely performed on all compounds possessing labile hydrogens.

7,8-Dimethoxy-*N*-methylcyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline Hydrobromide (2). After refluxing 2.45 g (0.0105 mol) of 1[3] in 8.12 mL of 88% HCO_2H and 4.96 mL of formalin for 6 h, the acidic solution was washed into a separatory funnel and made alkaline with concentrated ammonium hydroxide. The solution, containing a precipitate, was extracted with ether and the ether was distilled leaving a cherry red oil. The hydrobromide salt of the oil yielded a solid after drying which was recrystallized from the ethyl acetate–absolute ethanol to give **2** (1.42 g) (41%), mp 228.5–230 °C. Anal. ($C_{15}H_{22}BrNO_2$) C, H, Br, N.

7,8-Dimethoxy-*N*-(2-methylbutyl)cyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline Hydrobromide (3). To 4.5 g (0.052 mol) of 2-methylbutyraldehyde refluxing in 150 mL of benzene, 4.06 g (0.017 mol) of 1[3] in 125 mL of benzene was added slowly. After refluxing into a Dean-Stark trap and removing 0.2 mL of water, the solvent was removed and the dark red oil remaining was dissolved in 55 mL of glacial acetic acid and hydrogenated at 45 psi over 0.5 g of PtO_2. The exhausted catalyst was removed by filtration through Celite and washed with methanol and the acid filtrate was made basic with aqueous NaOH. The product was extracted with ether from this basic solution while salting out with NaCl until no color was given by the extract with Dragendorf's reagent. Thorough removal of the ether gave 4.98 g of a cherry red oil which was dissolved in anhydrous isopropyl ether and the HCl salt prepared. Attempts to recrystallize the resulting sticky solid were unsuccessful. The salt was converted back to the free base and the resulting dark red oil distilled under high vacuum giving a cherry red liquid (0.02 g). This oil was dissolved in benzene and HBr gas was added; no precipitation occurred. The solvent was removed and the yellow oil was dried overnight which hardened it considerably and allowed the isolation of a powder on stirring under anhydrous ether. This powder was recrystallized from ethyl acetate yielding 1.17 g (16%) of the hydrobromide salt (**3**), mp 139.5–142 °C. Anal. ($C_{19}H_{30}BrNO_2$) C, H, Br, N.

7,8-Dimethoxy-*N*-(3,4-dimethoxybenzoyl)cyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline (4). The acid chloride of 3,4-dimethoxybenzoic acid was prepared by the general method described under compound **9** from 2.0 g (0.011 mol) of the acid. After overnight refluxing of 2.30 g (0.010 mol) of the tricyclic amine 1[3] with 3,4-dimethoxybenzoyl chloride and 6 mL of triethylamine in 250 mL of benzene, the reaction mixture was cooled and washed with 2 × 150 mL of H_2O, 2 × 100 mL of 10% H_2SO_4, 2 × 100 mL of 10% NaOH, and finally 2 × 100 mL of H_2O. Removal of the solvent gave 4.15 g of an amber oil which possessed a very intense amide carbonyl absorption in the IR. This compound was purified by chromatographing twice on silica gel as described under compound **9**. Some fractions contained carbonyl absorptions at 1720 cm^{-1} (indicative of the presence of unreacted carboxylic acid). By this method, 1.12 g (29%) of **4** was obtained as a very viscous oil. Anal. ($C_{23}H_{27}NO_5$) C, H, N.

7,8-Dimethoxy-*N*-(3,4-dimethoxybenzyl)cyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline Hydrochloride (5). To 0.8 g (0.021 mol) of $LiAlH_4$ in 100 mL of anhydrous ether was added 2.25 g (0.0057 mol) of **4** dropwise in 100 mL of ether. After refluxing overnight, 3.0 g of Celite filter aid was added, followed by the dropwise addition of 5–6 mL of H_2O. The ether was decanted and the white precipitate was washed with ether several times, followed by decantation and finally filtration. Removal of the solvent from the filtrate yielded 1.85 g of an oil which showed absence of the carbonyl amide absorption in the IR. The hydrochloride salt of the oily amine was prepared, giving 2.01 g of **5** which recrystallized well from acetonitrile giving 1.36 g (57%): mp 222.5–224 °C. Anal. ($C_{23}H_{20}ClNO_4$) C, H, Cl, N.

7,8-Dimethoxy-*N*-(3,4-dimethoxyphenylacetyl)cyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline (6). In 75 mL of benzene and 5–6 mL of triethylamine, 2.45 g (0.0105 mol) of 1[3] and 2.36 g (0.011 mol) of 3,4-dimethoxyphenylacetyl chloride were refluxed overnight. The reaction solution was cooled and washed with 150 mL of water, 2 × 100 mL of 10% H_2SO_4, 2 × 100 mL of 10% NaOH, and finally 150 mL of H_2O. The solvent was removed on the rotary evaporator yielding 4.08 g of a viscous oil which resisted attempts at recrystallization. The oil was purified by column chromatography as described for compound **9**. The oil was isolated from the 25:75 benzene–chloroform fractions giving 1.68 g (39%) of **6**. Anal. ($C_{24}H_{29}NO_5$) C, H, N.

7,8-Dimethoxy-*N*-(*β*-3,4-dimethoxyphenylethyl)cyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline Hydrobromide (7). To 0.5 g (0.013 mol) of $LiAlH_4$ in anhydrous ether was added dropwise 1.27 g (0.0034 mol) of **6** in ether. After refluxing for 24 h, 1.5 g of Celite filter aid was added and excess $LiAlH_4$ was decomposed, with cooling, by the very slow addition of water. The resulting precipitate was washed with ether, followed by decantation several times, and then the precipitate was filtered. Removal of the solvent from the ether filtrate on the rotary evaporator gave 1.22 g of a light pink oil which showed no carbonyl absorption in the IR. The HBr salt was prepared and recrystallized from acetonitrile giving 1.05 g (71%) of **7** as a white solid, mp 234–236 °C. Anal. ($C_{24}H_{32}BrNO_4$) C, H, Br, N.

7,8-Dimethoxy-*N*-(2,2-diphenylethyl)cyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline (8). In 150 mL of benzene, 2.12 g (0.009 mol) of 1[3] and 3.0 g (0.015 mol) of diphenylacetaldehyde were refluxed overnight with removal of H_2O in a Dean-Stark trap. After removal of the solvent on the rotary evaporator, the residual red oil was dissolved in 75 mL of glacial acetic acid and hydrogenated over 0.6 g of PtO_2 at 45 psi. The exhausted catalyst was filtered and the solvent removed by rotary evaporation. The resulting oil was treated with dilute HCl and the HCl solution made basic with NaOH, the resulting oily precipitate was extracted with ether, and the ether was dried over Na_2SO_4 and removed by distillation giving 3.11 g of an orange-red oil. This oil was dissolved in benzene and treated with HBr gas to give a hard glassy solid upon removal of the benzene which did not crystallize after many attempts. The material was dissolved in acetonitrile–ethyl acetate, the volume reduced on the steam bath, and on cooling a black tarry precipitate was obtained. The solvent was removed and the free base extracted with ether after treating the residue with aqueous NaOH. Removal of the ether yielded a darkly colored glass which was chromotographed on silica gel under the same conditions as outlined for compound **9**. A light-colored oil was obtained (in the 25:75 benzene–chloroform fractions) which crystallized from methanol giving 1.07 g (28%) of **8** as prisms, mp 100–102 °C. Anal. ($C_{28}H_{31}NO_2$) C, H, N.

7,8-Dimethoxy-*N*-(*β*,*β*-diphenylpropionyl)cyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline (9). *β*,*β*-Diphenylpropionyl chloride was prepared by refluxing 2.45 g (0.016 mol) of *β*,*β*-diphenylpropionic acid with a large excess of $SOCl_2$ in benzene. After removing the $SOCl_2$, the resulting acid chloride, 2.45 g (0.0105 mol) of 1,[3] and 4.0 mL of triethylamine were refluxed in benzene for 7–8 h. The reaction mixture was cooled, rinsed into a separatory funnel, and washed with 150 mL of H_2O, 2 × 100 mL of 15% H_2SO_4, 2 × 100 mL of 10% NaOH, and 2 × 100 mL of H_2O. The benzene solution was dried over anhydrous Na_2SO_4 and the solvent was thoroughly removed on the evaporator giving a viscous oil which was further dried in a vacuum oven. The oil did not solidify and all attempts to recrystallize it failed. The IR spectrum and a high-pressure liquid chromatogram indicated the presence of only minor impurities. Column chromatography on silica gel gave a pure material using 5 × 100 mL of benzene, 2 × 100 mL of 75:25 benzene–chloroform, 2 × 100 mL of 50:50 benzene–chloroform, and 25:75 benzene–chloroform as eluting solvents. The amide began eluting in the 25:75 benzene–chloroform and was isolated from 800 mL of the 25:75 benzene–chloroform eluent. Removal of the solvent and thorough drying gave an analytical sample of **9** as an extremely viscous oil, 1.81 g (27%). Anal. ($C_{29}H_{31}NO_3$) C, H, N.

7,8-Dimethoxy-*N*-(3,3-diphenylpropyl)cyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline (10). To a slurry of 2.0 g (0.053 mol) of $LiAlH_4$ in 100 mL of dry ether was added 2.96 g (0.0067 mol) of **9** in 100 mL of ether. After refluxing for about 20 h, adding 5.0 g of Celite filter aid, and decomposing excess hydride by the careful addition of 15 mL of H_2O, the white precipitate was filtered after the ether solution was decanted several times and the precipitate washed with ether. The ether extract was thoroughly evaporated on a rotary evaporator.

Recrystallization of the resulting solid from methanol gave **10** as prisms: 1.64 g (54%); mp 105–106.5 °C. Anal. ($C_{29}H_{33}NO_2$) C, H, N.

7,8-Dihydroxy-*N*-methylcyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline Hydrobromide (11). After refluxing 2.0 g (0.0061 mol) of **2** for 2 h under nitrogen in 25 mL of 48% HBr, the solution was evaporated to dryness on the rotary evaporator. Drying was completed in a vacuum oven at about 60 °C. Excess acetonitrile was necessary to dissolve the product and upon reducing the volume by approximately two-thrids, crystallization occurred. Recrystallization from acetonitrile and decolorizing with activated charcoal gave 0.78 g (43%) of **11**, mp 242–244 °C. Anal. ($C_{13}H_{18}BrNO_2$) C, H, Br, N.

7,8-Diacetoxy-*N*-methylcyclopentano[*f*]-1,2,3,4-tetrahydroisoquinoline Trifluoroacetate (12). To 1.0 g (0.0033 mol) of **11** in 5.0 g (0.083 mol) of glacial acetic acid was added 18 g of trifluoroacetic anhydride. Heat was evolved when the anhydride was added, accompanied by dissolution of **11**. After stirring 0.5 h and refluxing overnight, hydrogen bromide gas was bubbled through the reaction solution for 1 min; the volatile components were then removed on the rotary evaporator. The resulting oil was dried in the vacuum oven at 60–70 °C in the presence of fresh P_2O_5 for several days, and the resulting viscous material was stirred with a glass rod in anhydrous ether until it began to form small crystals which were recrystallized from ethanol–ether solution. Several recrystallizations from this solvent system and a decolorization with activated charcoal in absolute ethanol gave 0.59 g (42%) of **12**, mp 169.5–172 °C. Anal. ($C_{19}H_{22}F_3NO_6$) C, H, F, N.

5,6-Dimethoxy-*N*-methylcyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline Hydrobromide (14). In 16 mL of formic acid and 10 mL of formalin, 4.66 g (0.020 mol) of the tricyclic amine **13**[3] was refluxed for 6 h and stirred over the weekend. After pouring the reaction mixture into ice, 25 g of NaOH in water at 5 °C was added and the precipitate formed was extracted with ether. The precipitated salt was filtered and dried in the vacuum oven giving 6.25 g of a white powder. Ethanol–ether recrystallization of this material yielded 0.95 g (45%) of **14**, mp 133–136 °C. Anal. ($C_{15}H_{22}BrNO_2$) C, H, Br, N.

5,6-Dimethoxy-*N*-(2-methylbutyl)cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline Hydrobromide (15). In 70 mL of benzene, 2.26 g (0.0096 mol) of the tricyclic amine **13**,[3] 1.20 g (0.0099 mol) of α-methylbutyryl chloride, and 5–6 mL of triethylamine were refluxed for 30 h. After cooling and pouring the reaction mixture into a separatory funnel, it was washed with H_2O, 10% HCl, 5% NaOH, and again with H_2O. The solvent was thoroughly removed on the rotary evaporator giving 2.91 g of the amide which, after thorough drying, was reduced in 250 mL of isopropyl ether and 60 mL of anhydrous ether by 1.0 g (0.026 mol) of $LiAlH_4$ with refluxing for 48 h. To this mixture 5.0 g of Celite and 5–10 mL of H_2O were added dropwise with cooling in an ice bath, followed by filtration of the white salts. Washing with ether and evaporation of the solvent on the rotary evaporator yielded 2.64 g of a lightly colored oil. The hydrobromide salt was made in the usual way by precipitating the amine from ether by slow addition of HBr gas dissolved in dry ether. The salt was dissolved in excess ethyl acetate, boiled with activated charcoal, and filtered and the volume of the solvent was reduced causing the material to crystallize. From this, 1.77 g (47%) of the salt **15** was obtained, mp 156.5–158 °C. Anal. ($C_{19}H_{30}BrNO_2$) C, H, Br, N.

5,6-Dimethoxy-*N*-(3,4-dimethoxybenzoyl)cyclopentano-[*h*]-1,2,3,4-tetrahydroisoquinoline (16). A solution of 2.00 g (0.0086 mol) of **13**,[3] 5–6 mL of triethylamine, and 1.72 g (0.0086 mol) of 3,4-dimethoxybenzoyl chloride in benzene was refluxed for 24 h. After cooling, the reaction mixture was poured into a separatory funnel and washed with water, 10% HCl, 12% NaOH, and water. The solvent was thoroughly removed on the rotary evaporator giving 3.60 g of an oil which was purified by column chromatography on silica gel using 500 mL of benzene, 200 mL of 75:25 benzene–chloroform, 1100 mL of 50:50 benzene–chloroform, and 800 mL of 75:25 benzene–chloroform as eluting solvents. The material which came off the column in the 50:50 chloroform–benzene fraction was boiled with activated charcoal in 90–120 °C ligroine, filtered, and reduced in volume. The desired amide **16** crystallized as a white powder: 1.25 g (39%); mp 106–108 °C. Anal. ($C_{23}H_{27}NO_5$) C, H, N.

5,6-Dimethoxy-*N*-(3,4-dimethoxybenzyl)cyclopentano-[*h*]-1,2,3,4-tetrahydroisoquinoline Hydrobromide (17). A solution of 1.06 g (0.0026 mol) of **16** and 1.0 g (0.026 mol) of $LiAlH_4$ in anhydrous ether was refluxed for about 48 h. After cooling and adding 5.0 g of Celite, followed by 8 mL of H_2O added dropwise with caution, the ether was decanted and the white salts were washed with ether, followed by decantation and filtration. Removal of the solvent gave 0.86 g of a colorless oil. The hydrobromide salt was formed in the usual manner and yielded an analytical sample of **16** by simple filtration from the salt-forming solbution: 0.84 g (68%); mp 226–228.5 °C. Anal. ($C_{23}H_{30}BrNO_4$) C, H, Br, N.

5,6-Dimethoxy-*N*-(3,4-dimethoxyphenylacetyl)cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline (18). In 70 mL of benzene, 1.5 g (0.0064 mol) of **13**,[3] 1.38 g (0.0064 mol) of 3,4-dimethoxyphenylacetyl chloride (distilled carefully under high vacuum just before use), and 2 mL of triethylamine were refluxed for 20 h. The reaction mixture was cooled, poured into a separatory funnel, and washed with H_2O, 2 × 100 mL of 10% HCl, 2 × 100 mL of 8% NaOH, and 2 × 150 mL of water. After drying the solution over anhydrous Na_2SO_4 and removing the solvent on the rotary evaporator a viscous oil was obtained. Column chromatography of this oil on silica gel as previously described (compound **16**) gave a pure fraction (from the 50:50 benzene–chloroform eluate) which crystallized on standing to yield 310 mg (44%) of **18**, mp 101–102 °C. Anal. ($C_{24}H_{29}NO_5$) C, H, N.

5,6-Dimethoxy-*N*-(3,4-dimethoxyphenylethyl)cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline Hydrobromide (19). To 1.0 g (0.026 mol) of $LiAlH_4$ stirring in anhydrous ether, 1.0 g (0.0024 mol) of **18** in anhydrous ether was added slowly. Refluxing was continued for about 20 h. After decomposing excess $LiAlH_4$ as previously described (compound **17**), removing the solvent, and drying the residual oil, the oil was dissolved in ether and the HBr salt prepared. The product was recrystallized from acetonitrile giving 262 mg (22%) of the hydrobromide salt **19**, mp 235–236 °C. Anal. ($C_{24}H_{32}BrNO_4$) C, H, Br, N.

5,6-Dimethoxy-*N*-(diphenylacetyl)cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline (20). In 50 mL of dry benzene, 1.50 g (0.0064 mol) of **13**,[3] 1.48 g (0.0064 mol) of diphenylacetyl chloride (freshly distilled), and 2 mL of triethylamine were refluxed for about 21 h. After cooling, the contents of the reaction flask was rinsed into a separatory funnel with benzene and washed with H_2O, 2 × 100 mL of 10% HCl, 2 × 100 mL of 8% NaOH, and then water. The remaining benzene solution was dried over Na_2SO_4 giving a lightly colored viscous oil (2.37 g). This oil was chromatographed on a silica gel column under the same conditions as described for compound **17**, giving 1.63 g (59%) of the desired amide **20** as a viscous oil. Anal. ($C_{28}H_{29}NO_3$) C, H, N.

5,6-Dimethoxy-*N*-(2,2-diphenylethyl)cyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline (21). After refluxing 2.52 g (0.011 mol) of the tricyclic amine **13**[3] and 4.24 g (0.028 mol) of diphenylacetaldehyde in 150 mL of benzene for about 24 h, the solvent was removed on the rotary evaporator. The oil thus obtained was dissolved in 30 mL of glacial acetic acid and hydrogenated over 0.5 g of Pd/C at 40 psi for 48 h. After removing the catalyst by filtering through Celite and rinsing with CH_3OH, the solvents were removed on the rotary evaporator. The remaining oil was dissolved in CH_3OH and treated with cold NaOH solution giving a precipitate which was extracted with ether. An NMR spectrum of the material obtained after distillation of the ether indicated incomplete hydrogenation. Hydrogenation was repeated as before using 0.5 g of PtO_2 as catalyst rather than Pd/C. The oil obtained from this reaction showed hydroxyl absorption in the IR and probably contained some diphenylethanol. A hydrobromide salt was made in anhydrous ether giving 3.02 g of a tan powder. Attempts were made to recrystallize this salt and were initially unsuccessful. Conversion of the salt back to the free base yielded an oil which crystallized from absolute ethanol giving 1.35 g (30%) of the desired amine **21**, mp 116.5–118 °C. Anal. ($C_{28}H_{31}NO_2$) C, H, N.

5,6-Dihydroxy-*N*-methylcyclopentano[*h*]-1,2,3,4-tetrahydroisoquinoline Hydrobromide (22). Following reflux of 2.0 g (0.0061 mol) of **14** in 20 mL of 48% HBr for 2 h, the water–acid solvent was removed on the rotary evaporator and the residual solid was dried in the vacuum oven in the presence of P_2O_5. The salt was found to crystallize from water but water 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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A New Type of Anticonvulsant: 1-Aryl-3-oxotetrahydroisoquinolines[1]

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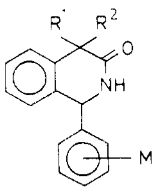
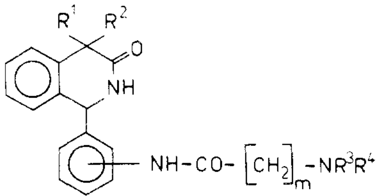
Thirty-two 1-aryl-3-oxotetrahydroisoquinolines have been prepared in which the 2′- or 4′-substituents are (*N*-alkylaminoacyl)amino derivatives. Several derivatives were found to have anticonvulsant properties. A structure–activity relationship study was carried out.

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.



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

3, $R^1 = R^2 = H$; $M = 4'-NH_2$



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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**).