fluxed in 0.2 *N* methanolic HCl (15 ml, prepared by diluting 1.0 *N* HCl with MeOH). The solution was evaporated to dryness *in vacuo*, and the semicrystalline residue crystallized (EtOH–Et_2O). A yield of 0.099 g (61%) of crystalline material was obtained; mp 173–175° (a different crystalline form has mp 158–160°); λ_{max} 291 mμ (ϵ 9.1 × 10^3) in 0.1 *N* HCl; λ_{max} 244 mμ (ϵ 6.2 × 10^3), 309 mμ (ϵ 6.6 × 10^3) in 0.1 *N* NaOH. *Anal.* ($C_{19}H_{26}ClNO_4$) C, H.

α^4,α^5-O-Isopropylidine-α^3-O-adamantoylpyridoxol Hydrochloride (IV).—α^4,α^5-O-Isopropylidenepyridoxol[8] (750 mg) was dissolved in 25 ml of pyridine and 1 g of adamantoyl chloride in 25 ml of pyridine was added. After refluxing for 0.5 hr and evaporation *in vacuo*, the residue was extracted with ether, filtered, dried, and treated with ethereal HCl. The hydrochloride was filtered and was washed (Et_2O), yield 1.47 g, mp 176–180° which was raised to 183–184° after recrystallization from C_6H_6–Et_2O. *Anal.* ($C_{22}H_{30}ClNO_4$) C, N.

The free base had mp 140–142° (from petroleum ether, bp 37–54°).

α^4-O-Adamantoylpyridoxol Hydrochloride (V).—α^4,α^5-O-Isopropylidene-α^3-O-adamantoylpyridoxol (free base from IV, 548 mg) was dissolved in methanolic HCl containing 10% H_2O, and was heated at 65–70° for 1 hr. The solution was evaporated to dryness, the residue was dissolved in EtOH, and the resulting solution was evaporated again. After recrystallization (EtOH–Et_2O), the yield was 373 mg (76%); mp 182–183°; λ_{max} 293 mμ (ϵ 8.3 × 10^3) in 0.1 *N* HCl; λ_{max} 243 mμ (ϵ 6.4 × 10^3), λ_{max} 309 mμ (ϵ 6.8 × 10^3) in 0.1 *N* NaOH. *Anal.* ($C_{19}H_{26}ClNO_4$) C, H. When the hydrolysis was conducted in 0.1 *N* aqueous HCl, the yield was reduced to 17%.

Acknowledgments.—This study was supported by a research grant (CA-08793) from the National Cancer Institute, U. S. Public Health Service. We wish to thank Dr. Charles A. Nichol for his encouragement and interest.

Isoquinolines as Cholinesterase Inhibitors. I

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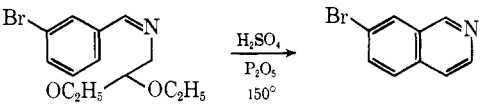
In our synthetic work on isoquinolines, it became apparent that any cholinesterase inhibitory properties of these molecules may be of interest in comparison with simple aliphatic or monocyclic amines. Although bis-quaternary quinolines[1] and isoquinolines[2] have been evaluated as cholinesterase inhibitors, tetrahydro- and decahydroisoquinolines have not been reported to be active. Several substituted isoquinolines and their hydrogenated derivatives have been prepared and evaluated against human plasma cholinesterase in an initial screening program which will precede further study.

The synthesis of isoquinolinecarboxylic acids, by way of a Pomeranz–Fritsch ring closure of 3-bromobenzalaminoacetal, as outlined by Tyson,[3] was followed. However, instead of a mixture of 5- and 7-isoquinolinecarboxylic acids being produced, as reported by Tyson, we were able to isolate only one product. In order to identify the product from the above synthesis, 5-isoquinolinecarboxylic acid was synthesized from 5-nitroisoquinoline as outlined in the Experimental Section. Mixture melting point, analytical, and gas chromatographic data of a number of derivatives of 5-carbomethoxyisoquinoline and the corresponding derivative, prepared by the Tyson synthesis, indicated that the Pomeranz–Fritsch ring closure in the Tyson synthesis had taken place specifically at the 6 position of the 3-bromobenzalaminoacetal, resulting, exclusively, in the formation of 7-isoquinolinecarboxylic acid.



The tetrahydro and decahydro derivatives of the methyl esters of both the 5- and 7-isoquinolinecarboxylic acids were prepared as described in the Experimental Section. Complete hydrogenation under low-pressure conditions proceeded smoothly;[4] more difficulty was experienced in hydrogenating the 5-methyl ester to the decahydro derivative than the corresponding 7 isomer. The 5-acetoxy derivatives were synthesized to evaluate the influence of position and nature of the carboxy group on cholinesterase inhibition. During the complete hydrogenation of 5-acetoxy-2-ethylisoquinolinium bromide (I) in glacial acetic acid containing sulfuric acid, hydrogenolysis and condensation of two molecules of the resulting decahydro alcohol occurred yielding a bis(2-ethyldecahydroisoquinoline) ether. This finding complements our evidence outlined in an earlier communication.[4] Furthermore, conversion of I to its corresponding quaternary hydroxide, followed by hydrogenation under identical conditions, yielded 5-hydroxy-2-ethyldecahydroisoquinoline, substantiating our earlier contention[4] of the involvement of the halide ion in this ether condensation.

Biological Activity.—Four series of substituted isoquinolines were screened as cholinesterase inhibitors. Manometric determinations were carried out on a GME-Lardy RWB-3 Warburg instrument at concentrations of 1 × 10^{-3} *M*. Further details of the procedure have been outlined by Beasley, *et al.*[5] For the synthesis of compounds not reported here see ref 4. The biological results are shown in Tables I and II. The data in Tables I and II indicate that the hydrogenated compounds possess greater inhibitory properties, the greatest inhibition being associated with the fully saturated compounds. This trend may involve the "semiflexible" nature of the more saturated compounds as compared with the more rigid flat structures associated with the unsaturated compounds as well as the greater degree of hydrophobicity of the more saturated molecules. Evidence for some hydrophobic sites in adenosine deaminase has recently been presented[6] and Augustinsson's[7] work may imply the presence of similar sites in cholinesterase. The significant increase in enzyme inhibition produced by the 3,4,5-trimethoxybenzoyl esters compared with the corresponding free hydroxy compounds is evident (Table I). Derivatives of the isoquinolinecarboxylic acid (Table II) do not seem to possess any significant ac-

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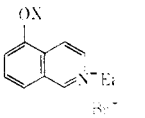
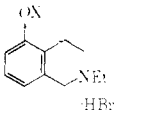
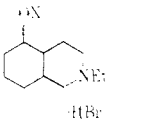
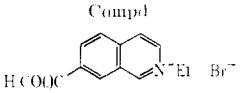
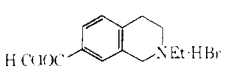
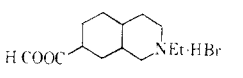
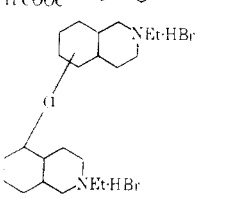
TABLE I
PERCENTAGE INHIBITION OF HUMAN PLASMA CHOLINESTERASE SUBSTITUTED ISOQUINOLINES AT 1×10^{-5} *M* CONCENTRATION[a]

Compd	% inhib — X — H	% inhib — X — 3,4,5-Trimethoxybenzoyl	% inhib — X — CH$_3$CO
	47.6	*b*	49.1
	58.9	70.2	61.1
	67.2	85.3	*c*

[a] Cited values represent the average of duplicate determinations within 5% of each other. [b] Too insoluble for evaluation. [c] Salt unstable in solution.

TABLE II
PERCENTAGE INHIBITION OF HUMAN PLASMA CHOLINESTERASE BY SUBSTITUTED ISOQUINOLINES AT 1×10^{-5} *M* CONCENTRATION[a]

Compd	% inhib
	38.5
	26.5
	33.8
	83.2

[a] Cited values represent the average of duplicate determinations within 5% of each other.

tivity, whereas the "reversed esters," *i.e.*, acetoxy compounds, possess inhibitory properties.

Experimental Section

All melting points were determined using a Swissco melting point apparatus and are corrected. Elemental analyses were carried out by Drs. G. Weiler and F. B. Strauss, Oxford, England. Ultraviolet spectra were determined in water on a Perkin-Elmer Model 202 spectrophotometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values.

7-Isoquinolinecarboxylic Acid.—The synthesis outlined by Tyson[3] was carried out and yielded only 7-isoquinolinecarboxylic acid.

7-Carbomethoxyisoquinoline.—7-Isoquinolinecarboxylic acid hydrochloride (20 g) and $SOCl_2$ (200 ml) were refluxed for 30 min on a steam bath. The resulting mixture was evaporated to dryness to yield a dark solid which was treated with anhydrous MeOH (100 ml) under reflux for 15 min. The excess methanol was removed, and the residue was dissolved in water and decolorized with charcoal. The solution was made alkaline with $KHCO_3$ and extracted with ether. The ether was dried and evaporated to yield 11.2 g (63%) of light brown oil which crystallized (overnight) in the refrigerator; mp 96–98° (lit.[3] 100°). Thin layer and gas chromatography of this ester indicated a single component.

7-Carbomethoxy-2-ethylisoquinolinium Bromide.—7-Carbomethoxyisoquinoline (8.5 g), absolute EtOH (100 ml), and excess EtBr (8.4 g) were refluxed on a steam bath for 8 hr. Excess solvent and EtBr were distilled, and the residual solid was recrystallized from EtOH to yield 12.6 g (93%) of the quaternary salt, mp 217.0–218.6°, λ_{max} 236 mμ (log ε 4.9). *Anal.* ($C_{13}H_{14}BrNO_2$) C, H, Br, N.

7-Carbomethoxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide.—7-Carbomethoxy-2-ethylisoquinolinium bromide (1.5 g) in absolute EtOH (100 ml) was hydrogenated at 2.81 kg cm^2 (PtO_2, 100 mg) for 8 hr. The white solid which had separated was redissolved by warming. The catalyst was filtered from the hot solution which was then concentrated. Colorless plates (750 mg) crystallized on cooling; mp 215.2–216.1°, λ_{max} 238 mμ (log ε 4.2). *Anal.* ($C_{13}H_{18}BrNO_2$) C, H, Br, N.

7-Carbomethoxy-2-ethyldecahydroisoquinoline Hydrobromide.—7-Carbomethoxy-2-ethylisoquinolinium bromide (1.5 g), AcOH (30 ml), and concentrated H_2SO_4 (0.15 ml) were hydrogenated (PtO_2, 1.5 g) for 48 hr at 3.52 kg/cm^2. The catalyst was filtered. The filtrate was diluted (H_2O, 25 ml), made alkaline with NaOH, and extracted with ether. The dried extract was evaporated to yield a pale yellow oil (0.75 g) which gave a hydrobromide salt that was recrystallized (EtOH–Et_2O); mp 205.4–206.0°. The uv spectrum of this compound showed no maxima from 220–360 mμ. *Anal.* ($C_{13}H_{24}BrNO_2$) C, H, Br, N.

5-Acetoxy-2-ethylisoquinolinium Bromide.—5-Hydroxyisoquinoline (9.1 g) in 2 *N* NaOH (125 ml) was shaken with Ac_2O (16.4 g), and an equal volume of crushed ice. The separated, yellow oil was extracted with ether which was dried and evaporated to yield 11.8 g of a pale yellow oil that solidified on standing. This 5-acetoxyisoquinoline (11.8 g), absolute EtOH, and excess EtOH (11.8 g) were refluxed for 8 hr. The solvent and excess EtBr were removed under vacuum, and the residual, yellow solid (15.9 g) was recrystallized (EtOH); mp 212.0–213.0°. *Anal.* ($C_{13}H_{14}BrNO_2$) C, H, Br, N.

5-Acetoxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide.—5-Acetoxy-2-ethylisoquinolinium bromide (4 g) and absolute EtOH (13 ml) were hydrogenated at 3.16 kg/cm^2 (PtO_2, 0.4 g). The filtered solution was evaporated to yield a viscous oil which crystallized from EtOH; yield 1.1 g of white solid, mp 223.0–224.2°. Ir and mixture melting point data[4] indicated this compound to be 5-hydroxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline hydrobromide. It was dissolved in 2 *N* NaOH and was shaken with an equal volume of ice and excess Ac_2O. The solution was extracted with ether. The ether was dried and the hydrobromide formed in the usual manner. It was crystallized from EtOH–Et_2O; mp 176.2–178.0°. *Anal.* ($C_{13}H_{18}BrNO_2$) C, H, Br, N.

5-Isoquinolinecarboxylic Acid.—5-Nitroisoquinoline (12.5 g) in MeOH (300 ml) was hydrogenated at low pressure and room temperature (10% Pd–C, 1.25 g, 2 hr). The filtered solution was evaporated to yield 5-aminoisoquinoline as a light brown solid which was crystallized from $CHCl_3$–petroleum ether to yield 10.6 g, mp 121.5–123.0° (lit.[5] 124–125°). This 5-aminoisoquinoline (4.8 g) was dissolved in 48% HBr (12 ml) and H_2O (13 ml). The solution was cooled, and a cold solution of $NaNO_2$ (2.3 g in 15 ml of water) was added. The mixture was allowed to warm to room temperature and added slowly to a stirred solution of CuBr (5.8 g) in 48% HBr maintained about 50°. After 24 hr the solution was made alkaline with NaOH and the resulting mixture was steam distilled to yield 5-bromoisoquinoline as a white solid (5.3 g). 5-Bromoisoquinoline (25 g) (from the steam distillation) was thoroughly mixed with CuCN (18.5 g) and heated for 45 min at 250°. The isoquinoline-5-nitrile was distilled (3 mm) from the reaction mixture; yield 10 g (70%), mp 138.0–139.0° (lit.[5] 139.0°). One gram of this nitrile was heated in a Carius tube with concentrated HCl (9 g) at 150° for 8 hr. The contents of the tube were then evaporated to dryness to yield 1.25 g (92%) of the hydrochloride of 5-isoquinolinecarboxylic acid (mp >300°).

5-Carbomethoxy-2-ethylisoquinolinium Bromide.—5-Isoquinolinecarboxylic acid hydrochloride (20 g) gave 11 g of 5-carbomethoxy-2-ethylisoquinolinium bromide as described for the 7 isomer; mp 183.0–183.5°. *Anal.* ($C_{13}H_{14}BrNO_2$) C, H, Br, N.

5-Carbomethoxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide.—5-Carbomethoxy-2-ethylisoquinolinium bromide (5 g) in 150 ml of absolute EtOH was hydrogenated as outlined for

[4] E. Ochiai and M. Ikehara, *J. Pharm. Soc. Japan*, **73**, 660 (1953).

the 7 isomer. Recrystallization of the product from EtOH yielded 4.0 g of white needles, mp 187.0–188.0°. *Anal.* ($C_{13}H_{18}BrNO_2$) C, H, Br, N.

5-Carbomethoxy-2-ethyldecahydroisoquinoline Hydrobromide.—5-Carbomethoxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline (1 g), AcOH (30 ml), and concentrated H_2SO_4 (0.1 ml) were hydrogenated (PtO_2, 1 g, 48 hr, 3.52 kg/cm²). The product was isolated in the usual manner, and the hydrobromide salt was prepared and recrystallized (EtOH–Et_2O) (0.3 g, mp 168.0–169.0°). The uv spectrum of this compound showed no absorption in the range 220–360 mμ. *Anal.* ($C_{13}H_{24}BrNO_2$) C, H, Br, N.

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Diimides of Cyclobutane-1,1-dicarboxylic Acid[1a]

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Various imides of cyclobutanecarboxylic acid, particularly N-acetylcyclobutanecarboxamide, possess a structure-dependent ability to act as central nervous system depressants.[2] The phenomenon appears to be related to the cyclobutane ring system and is unique in that it is not subject to circadian rhythm variance, a finding contrary to the behavior of barbiturates. To further elucidate the biochemorphology of cyclobutane compounds we have expanded the original study to a group of cyclobutane-1,1-dicarboxylic acid derivatives. With the exception of **6**, a spirothiobarbiturate, these substances are di-N-acylimides and congeners of the compounds studied earlier.

When bioassayed the compounds were tested as reported previously[2] but dispersed in mineral oil, since they tended to agglomerate when ground in 0.25% methylcellulose. At a dose of 1000 mg/kg there was no loss of spontaneous activity nor were there any deaths. In addition to intraperitoneal administration, the compounds were also given orally as suspensions in gum tragacanth with the same lack of effect.

They were also tested as potentiators of barbiturate sedation[3,4] using pentobarbital sleeping time, judged by loss of the righting reflex, as a criterion. Using five mice and 50-mg/kg ip dose of the barbiturate, a mean sleeping time of 81 min was obtained. The only compound exhibiting potentiation was **6**. The mean sleeping time for five mice receiving 500 mg/kg of this compound orally 30 min before the standard dose of barbiturate was 147 min. A potentiation factor of 1.8 on the part of this compound at a dose which itself appears to have no depressant activity is of considerable practical and mechanistic interest.

Experimental Section

Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

Preparation of Diimides.—A mixture of 20 g of $SOCl_2$ and 5 g (0.034 mole) of cyclobutane-1,1-dicarboxylic acid was refluxed for 1.5 hr (hood) and excess $SOCl_2$ was removed by flash evaporation. Crude cyclobutane-1,1-dicarbonyl chloride (1.6 g, 0.009 mole) was added dropwise to a stirred and cooled solution of the amide (0.018 mole) in 10 ml of neutral alumina washed and KOH-dried pyridine. In every case an exothermic reaction ensued; when it subsided the mixture was heated on the steam bath for 1 hr. The reaction mixture was then poured onto 100 g of crushed ice and the product precipitated. Solvents used in crystallization and yields of the respective compounds are in Table I.

TABLE I

DIIMIDES OF CYCLOBUTANE-1,1-DICARBOXYLIC ACID

No.	R	Yield, %	Mp, °C[a]	Crystn[b] solvent	Formula	Analysis[c]
1	CH_3	40	215	C	$C_{10}H_{14}N_2O_4$	N
2	C_2H_5	50	243	A	$C_{12}H_{18}N_2O_4$	N
3	$C(CH_3)_3$	60	215	A	$C_{16}H_{26}N_2O_4$	N
4	$(CH_2)_4CH_3$	50	175	E	$C_{18}H_{30}N_2O_4$	N
5		45	255	A	$C_{16}H_{22}N_2O_4$	N
6	>C=S	40	220	C	$C_7H_8N_2O_2S$	C, H, N

[a] Corrected. [b] A, acetone; B, benzene; C, chloroform; E, ethyl ether. [c] Analytical results obtained for the elements listed were within ±0.4% of the theoretical values.

Imidothiazoles

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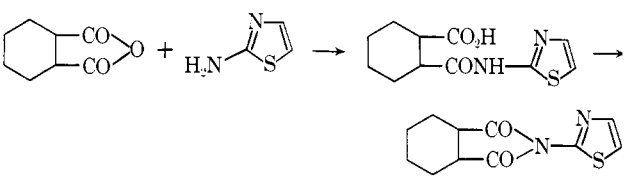
As part of a continuing study of various imides[2–4] and their reduction products as pharmacologically active compounds, we have prepared a limited series of imides derived from 2-aminothiazole and related thiazoles. These imides were obtained from a wide variety of compounds of diverse structure. An example employing 1,2-cyclohexanedicarboxylic anhydride illustrates the general method used (Scheme I). This reaction was either accomplished by heating an intimate

SCHEME I



(1) (a) Supported in part by research Grant NB-7548 of the National Institutes of Health, U. S. Public Health Service. (b) To whom inquiries should be directed.

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(1) Deceased, June 1967.

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