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Preparation and Cardiovascular Actions of a Group of Tetrahydroisoquinoline Derivatives†

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We have prepared a series of *N*-(alkylthioalkyl)tetrahydroisoquinolines and their sulfinyl and sulfonyl derivatives (Table I, compounds **1–13**) and have found particularly the ethyl-X-propyl analogs, where X = thio (**8**), sulfinyl (**9**), and sulfonyl (**10**), to produce distinctive and interesting hemodynamic effects apparently mediated by adrenergic mechanisms.[1,2,‡]

Experimental Section

Melting points were determined with a capillary melting point apparatus and are corrected for stem exposure. Microanalyses were performed by the Galbraith Laboratories, Knoxville, Tenn., and, unless indicated otherwise, are within ±0.4% of calculated values. Infrared spectra were determined with a Beckman Model IR-5 or IR-10 spectrophotometer and nmr spectra with a Varian Model A-60. Spectra were consistent with the assigned structures.

Most of the bases from which the salts listed in Table I were derived were characterized but, to save space and since the chemistry is unexceptional, the properties of only those obtained in the following illustrative procedures are indicated.

2-(Methylthiomethyl)-1,2,3,4-tetrahydroisoquinoline (1). Chloromethyl methyl sulfide (38.6 g, 0.4 mol) was added, dropwise with stirring, to a solution warmed to 35° of tetrahydroisoquinoline (106 g, 0.8 mol) in C_6H_6 (250 ml). A white precipitate formed during the addition. The reaction mixture was stirred at room temperature for 6 hr, tetrahydroisoquinoline hydrochloride (57.5 g, 85%) was separated, and the filtrate extracted with dilute HCl. The acid solution was made alkaline with NaOH and the precipitated oil dissolved in Et_2O. Drying and removal of the Et_2O left a yellow oil which was twice distilled to yield 29.8 g (39%) of **1**: bp 120–122° (1.0 mm); $n^{24}D$ 1.5819. *Anal.* ($C_{11}H_{15}NS$) S. The **hydrochloride salt** was recrystallized from EtOH–Et_2O. The **methanesulfonate salt,** recrystallized from EtOH–Et_2O, showed mp 116–118°. *Anal.* ($C_{12}H_{19}NO_3S_2$) S. Attempts to oxidize **1** to the sulfoxide were unsuccessful. Although salts of **1** were reasonably stable, they did decompose with release of MeSH on prolonged standing in aqueous solution.

2-(3-Chloropropyl)-1,2,3,4-tetrahydroisoquinoline (14). Tetrahydroisoquinoline (215 g, 1.6 mol) and trimethylene chlorobromide (126 g, 0.8 mol) in C_6H_6 (1300 ml) was stirred at room temperature for 100 hr. Tetrahydroisoquinoline hydrobromide (130 g, 75%) was filtered off. Work-up of the filtrate afforded 89 g (53%) of **14**: bp 131–137° (3 mm); $n^{24}D$ 1.5463. *Anal.* ($C_{12}H_{16}ClN$) N. The **hydrochloride salt,** recrystallized from *i*-PrOH–Et_2O, showed mp 187–187.5°. *Anal.* ($C_{12}H_{17}Cl_2N$) C, H, Cl.

2-(3-Ethylthiopropyl)-1,2,3,4-tetrahydroisoquinoline (8). To the solution obtained by dissolving Na metal (18.7 g, 0.81 g-atom) and ethanethiol (29.8 g, 0.48 mol) in EtOH (300 ml) was added, dropwise with stirring at room temperature, a solution of **14** hydrochloride (79.3 g, 0.32 mol) in MeOH (150 ml). The reaction mixture was stirred for 0.5 hr at room temperature followed by 1 hr at reflux. Work-up provided 61.5 g (81%) of **8**: bp 150–156° (0.4 mm); $n^{25}D$ 1.5521. *Anal.* ($C_{14}H_{21}NS$) N. The **hydrochloride salt** was recrystallized from *i*-PrOH.

2-(3-Ethylsulfinylpropyl)-1,2,3,4-tetrahydroisoquinoline (9). A solution of 19 g of commercial (FMC) 40% peracetic acid (0.1 mol) in MeCN (25 ml) was added, dropwise with stirring, to an ice-cold solution of 23.5 g (0.1 mol) of **8** and glacial AcOH (6 ml) in MeCN (50 ml). The reaction mixture was stirred for 1 hr at room temperature (higher yields of cleaner material were realized when the entire reaction was carried out at 5–10°), poured into H_2O (150 ml), and made basic with dilute aqueous NH_3 and the oil precipitate was dissolved in Et_2O. The Et_2O solution was washed, dried, and treated with ethereal HCl, and the resultant precipitate was recrystallized from *i*-PrOH to yield 13.4 g (47%) of **9** hydrochloride: mp 198–199°; ν_{max} (KBr) 1055 and 1018 cm^{-1} (sulfoxide).

2-(3-Ethylsulfonylpropyl)-1,2,3,4-tetrahydroisoquinoline (10). To a solution of 23.5 g (0.1 mol) of **8** in glacial AcOH (100 ml) was added, dropwise with stirring and maintenance of the temperature at about 30° by external cooling, 27.2 g of 50% H_2O_2 (0.4 mol). The solution was allowed to stand for 48 hr at room temperature, poured into H_2O (400 ml), made alkaline, and extracted with Et_2O. The Et_2O layer was washed, dried, and treated with ethereal HCl. Recrystallization of the precipitate from a mixture of *i*-PrOH and EtOH afforded 13.6 g (45%) of **10** hydrochloride: mp 226–228°; ν_{max} (KBr) 1303 and 1132 cm^{-1} (sulfone).

Discussion of Results

The compounds were screened pharmacologically in trained, unanesthetized, normotensive dogs using a tail cuff attachment to monitor blood pressure (see Table I for details). Tabulated results are relative effects on systolic blood pressure, from a significant decrease (more than 10% lasting for at least 1 hr) to a marked increase (at least a 30–40% increase with blood pressure remaining above normal for more than 3 hr). Compounds of interest from this screen, 2-(3-ethylsulfinylpropyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (**9**) in particular, were subjected to detailed pharmacological work-up.

The pharmacological profile of **9** is qualitatively illustrative of the compounds which significantly elevate systolic blood pressure. Its acute LD_{50} (iv, mice) is 77 mg/kg. **9**, at an iv dose of 1 mg/kg or an oral dose of 5 mg/kg administered to an unanesthetized, normotensive dog, increased systolic blood pressure a maximum of about 30% with blood pressure returning to normal in 3–5 hr, increased the heart rate a maximum of about 40%, but had little or no effect on diastolic blood pressure. Elevated systolic blood pressure could be maintained over a 5-day period in the unanesthetized dog given 1 mg/kg oral doses t.i.d.

In the anesthetized (pentobarbital) dog, at an iv dose of 1 mg/kg, **9** either had little effect or reduced mean arterial blood pressure, increased cardiac output (dye-dilution technique) a maximum of about 80% for a 45% maximum reduction in total peripheral resistance, and increased heart rate about 65% (maximum) and stroke volume about 30%. **9** increased the rate of blood flow through the femoral artery (Shipley-Wilson rotameter) at doses which had no effect on mean blood pressure.

Thus, the overall hemodynamic effects of **9** apparently are a resultant of a marked and prolonged increase in cardiac output coupled with vasodilatation and reduced peripheral resistance. These actions could be explicable in terms of α-adrenergic blockade coupled with β-adrenergic stimulation[3] and this view is supported by the finding that in the anesthetized dog in iv doses of 0.5–1 mg/kg, **9** blocked the α response and potentiated the β response to normally effective amounts of exogenous norepinephrine and epinephrine, respectively. The cardiac effects of **9** were blocked by the β-adrenergic blocking agent, propranolol. That, as seemed most probable, the β stimulation is indirect is indicated by the observation that **9** is ineffective as an agonist in reser-

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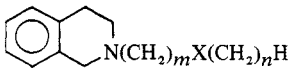
‡One of these compounds, 2-(3-ethylsulfinylpropyl)-1,2,3,4-tetrahydroisoquinoline (**9**), is currently undergoing clinical trial as an orally active agent against shock.

Table I. Tetrahydroisoquinolines



No.	*m*	*n*	X	Salt	Mp, °C	Formula	Analyses	Systolic blood pressure increase[a]
1	1	1	S	HCl	154–157	$C_{11}H_{16}ClNS$	C, H, Cl	0
2	2	1	S	HCl	185–187	$C_{12}H_{18}ClNS$	C, H, Cl	0
3	2	1	SO	HCl	169–170	$C_{12}H_{18}ClNOS$	C, H, Cl	0
4	2	1	SO_2	HCl	213–215	$C_{12}H_{18}ClNO_2S$	C, H, Cl	0
5	3	1	S	HCl	184–186	$C_{13}H_{20}ClNS$	H, Cl; C[b]	0
6	2	3	S	HCl	177–178	$C_{14}H_{22}ClNS$	C, H, Cl	0
7	2	3	SO	HCl	192–193	$C_{14}H_{22}ClNOS$	C, H, Cl	–
8	3	2	S	HCl	200.5–202	$C_{14}H_{22}ClNS$	C, H, Cl	2+
9	3	2	SO	HCl	198–199	$C_{14}H_{22}ClNOS$	C, H, Cl	2+
10	3	2	SO_2	HCl	226–228	$C_{14}H_{22}ClNO_2S$	C, H, Cl	2+
11	3	3	S	HCl	195–197	$C_{15}H_{24}ClNS$	C, H, Cl	1+
12	3	3	SO	HCl	189–190	$C_{15}H_{24}ClNOS$	C, H, Cl	1+
13	3	3	SO_2	HCl	205–206	$C_{15}H_{24}ClNO_2S$	C, H, Cl	1+

[a]Compound administered iv and po to at least three trained, unanesthetized, normotensive dogs and blood pressure measured indirectly through a tail cuff attached to a Beckman continuous systolic monitor or with an electrosphygmograph cuff attachment to a physiograph. Tabulated results are based on measurements of systolic blood pressure of dogs administered an oral dose of 5 mg/kg. (2+) = a maximum systolic blood pressure increase of 30–40% with blood pressure remaining above normal for more than 3 hr; (1+) = a maximum increase of *ca.* 20% lasting 1–2 hr; (0) = less than 10% maximum increase or decrease lasting for less than 1 hr; (–) = more than 10% decrease in blood pressure lasting for at least 1 hr. [b]C: calcd, 60.56; found, 60.14.

pinized dogs with depleted catecholamine stores. It should be noted that if **9** is in fact an indirect β agonist, it produces a remarkably prolonged indirect action. **9** did not influence the response to exogenous acetylcholine.

The structural features prerequisite to the blood pressure elevating action seem exquisitely specific. Thus, **8**, **9**, and **10** were all about equally effective in raising systolic blood pressure, although **9** was preferred on the basis of overall properties. However, alteration of the N substituent by moving the sulfur one carbon closer to the nitrogen while keeping chain length constant, *i.e.*, propylthioethyl (**6**) and propylsulfinylethyl (**7**), destroyed this activity as did shortening (**1–5**) the chain by even one carbon atom.[§] Lengthening the chain by one carbon reduced activity. It is not entirely clear from just what underlying property this structural requirement derives. It cannot simply be lipophilic-hydrophilic balance since thio (**8**), sulfinyl (**9**), and sulfonyl (**10**) all provide active derivatives. Other evidence[#] suggests that it cannot be entirely a question of size and shape of the substituent either. The lack of activity of **6** and **7**, which have what appears to be the optimal chain length, can most probably be attributed to the inductive, base-weakening effect of positioning the sulfur atom just 2 carbons away from the basic nitrogen.

Since, as has long been recognized, tetrahydroisoquinoline can be considered as a cyclized, and therefore conformationally more fixed, phenethylamine, it is especially intriguing to note that all departures from the tetrahydroisoquinoline nucleus also resulted in loss of activity.[#] The results suggest that the internuclear phenyl-nitrogen distance may be of importance and that the spatial arrangement provided by a cisoid conformation may be optimum. A normal phenethylamine would be expected to be most stable in an extended, transoid conformation. These considerations lead to the question, which we are pursuing,[4] of whether conformation may also be important to direct β- (and α-) stimulating action.

The question remains as to how **9** might induce its apparent indirect β-stimulatory action. Isolated tissue experiments have shown that **9** does not cause release of norepinephrine from nerve endings and is therefore not an indirect agonist in the classic sense.[**] Further, **9** continues to produce effective α blockade, but no longer causes β stimulation, in the spinal cat with its brain destroyed.[††] It thus appears that the indirect β stimulation may be centrally mediated. In this connection, note may be made of the strong evidence that has been accumulating indicating the presence of an α-adrenergic *inhibitory* nerve pathway in the central nervous system which acts to inhibit the vasomotor center and reduce the sympathetic outflow from it.[5] On the basis of these data it becomes most enticing to suggest that **9** may be an effective *central* as well as peripheral α-adrenergic blocking agent. Central α-adrenergic blockade of the inhibitory pathway would leave the vasomotor center free to send out an unchecked flow of sympathetic stimuli. Since α-adrenergic responses in the periphery are blocked, the resultant would be a prolonged, indirect β stimulation.

It is, of course, recognized that classic α-adrenergic blocking agents induce a "reflex" β stimulation, presumably in response to the initial, profound drop in blood pressure they cause. It does not appear likely, however, that the effect of **9** can be attributed to a reflex action, first, because there is no initial, marked drop in blood pressure, and, second, because of the strength and duration of the β stimulation. Moreover, a separate, centrally mediated β-stimulatory action has been attributed to at least one classic α-adrenergic blocking agent, phentolamine.[6] It may simply be that **9** is a relatively more effective central α-adrenergic blocking agent. This would be in accord with its relatively high degree of lipophilicity.

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[§]We should stress that systolic blood pressure is a dependent variable, a resultant particularly of cardiac output and blood vessel volume. More detailed evaluation of the actions of the shorter chain compounds **1–7** on various cardiovascular parameters indicates that these compounds, although quantitatively less active, exhibit qualitatively the same pharmacological properties as **9**. (Private communication from D. R. VanDeripe and R. M. Hopkins of Mallinckrodt Chemical Works. We thank Dr. VanDeripe for this information.)

[#]A. P. Gray, R. H. Shiley, D. E. Heitmeier, and J. D. Mier, unpublished results.

[**]D. R. VanDeripe, private communication.

[††]We thank Dr. E. Reit for this information and for valuable discussions.

Mrs. M. D. Napoli for generously providing the pharmacological information listed in Table I and discussed here.

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Antiasthma Agents. 1. 4-Oxo-4*H*-[1]benzothieno-[3,2-*b*]pyran-2-carboxylic Acid and 4-Oxo-4*H*-[1]benzofuro[3,2-*b*]pyran-2-carboxylic Acid

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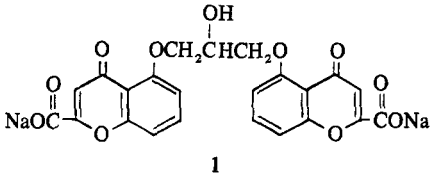
Disodium cromoglycate (**1**) is a substance which has shown very promising antiasthmatic properties.[1,2] We were interested in investigating other compounds for this type of activity, particularly those compounds that possessed a fused γ-pyrone ring, similar to that found in the chromone ring of disodium cromoglycate. We chose for synthesis and for biological study 4-oxo-4*H*-[1]benzothieno[3,2-*b*]pyran-2-carboxylic acid (**2**) and 4-oxo-4*H*-[1]benzofuro[3,2-*b*]pyran-2-carboxylic acid (**3**).



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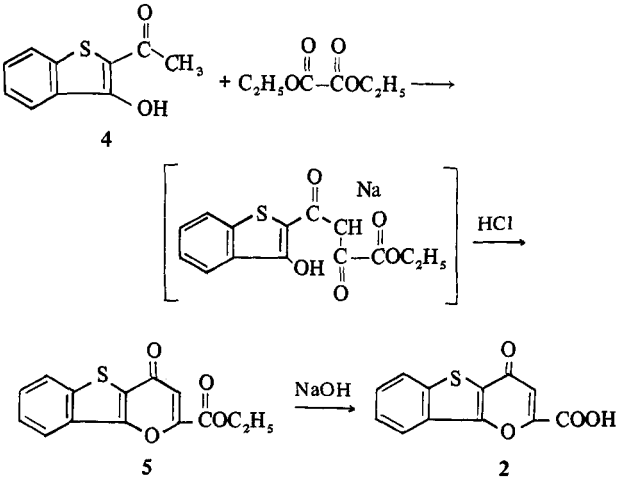
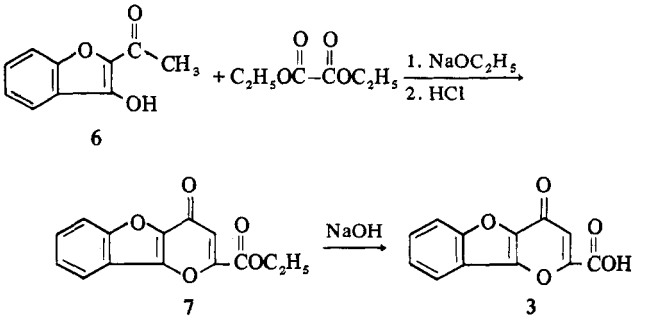
Chemistry. The only reference in the literature to the synthesis of 4-oxo-4*H*-[1]benzothieno[3,2-*b*]pyrans is that of Mustafa[3] who prepared 2-aryl derivatives by treatment of 3-hydroxybenzothienyl-2-methyl ketone[4] (**4**) with aromatic aldehydes followed by treatment of the resulting chalcone with selenium dioxide. We found that the desired 4-oxo-4*H*-[1]benzothieno[3,2-*b*]pyran-2-carboxylic acid (**2**) could be obtained readily in good yield from 3-hydroxybenzothienyl-2-methyl ketone[4] (**4**) by treatment with diethyl oxalate in the presence of sodium ethoxide to give the corresponding ester **5** (obtained in 71% yield) which, upon hydrolysis, gave the desired acid **2**.



4 5 2

A review of the literature disclosed no examples of the related 4-oxo-4*H*-[1]benzofuro[3,2-*b*]pyran heterocyclic system. We found that the desired 4-oxo-4*H*-[1]benzofuro-[3,2-*b*]pyran-2-carboxylic acid (**3**) could be obtained in an analogous way from 3-hydroxy-2-benzofuranyl methyl ketone[5] (**6**).



6 7 3

Biological Methods and Results. (A) Rats. **2** and **3** were tested in rats for their ability to inhibit the passive cutaneous anaphylaxis (PCA) reaction in animals passively sensitized to egg albumin as follows.[6] Rat homocytotropic antibody was elicited to egg albumin (EA) by the injection of 0.5 mg of EA + 0.5 cc of *H. pertussis* vaccine per rat. After 18-20 days the serum was collected and frozen until use. The antibody was shown to be of the 72-hr latency, heat labile type Five 0.1-ml vol of an appropriate dilution of this serum were inoculated into the shaved dorsal surface of a 200-g Sprague-Dawley rat. Saline controls were run also. After 72 hr the rat was challenged iv with 4 mg of EA + 0.5% Evans blue dye. In the case of drug-treated animals the materials were given iv at the time of antigen challenge or the materials were given ip 30 min before challenge with antigen. Results were reported as the inhibition of the number of spots per animal (regardless of size) that were seen at five dilutions of serum. The number of spots from a number of sensitization sites in drug-treated animals was compared with the spot score (number of total spots divided by the number of animals) obtained from the same number of sites in untreated animals. The per cent inhibition of the PCA reaction was then calculated.

The significance of the difference between treated and control in this PCA test has been analyzed and found to be significant with a P value of <0.001. The procedure is to find the highest dilution of the controls for which some of the animals do not have spots and some of the animals have spots. The number of animals not having spots at the next higher dilution of serum is counted and added to past control data. A new average is taken. We then graphed the probability of not getting a spot at this dilution *vs.* the sam-