65–70°. Crystallization from *i*-PrOAc gave *ca.* 60% recovery of compound: mp 69–72°. Crystallization from MeCN gave *ca.* 10% of product: mp 102–105°.

1,2,3,4-Tetrahydro-4-phenyl-1-naphthamide (20). The above mixture of nitriles as distilled, 28 g, 200 ml of 20% NaOH, and 300 ml of EtOH were refluxed and stirred for 8 hr, and the EtOH was then distilled. The aqueous layer was decanted and the rubbery residue was washed with H_2O and refluxed with 200 ml of H_2O and 300 ml of PhH until crystalline. The cooled mixture, filtered and washed, gave 16 g of amide: mp 170–173°. Recrystallization from MeCN with slight loss showed its mp was 179–181°. Concentration of the PhH liquor gave 7 g of a nitrile-free (*ca.* 1:1) mixture of the cis and trans amides: mp 125–140°. *Anal.* ($C_{17}H_{17}NO$) C, H, N.

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Synthesis and Pharmacological Properties of 5a,6,7,8,9,10,10a,11-Octahydrobenzo[*b*]cyclohepta[*e*]-[1,4]thiazine Derivatives

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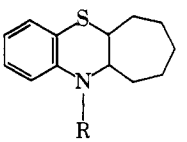
In the course of our earlier studies on sulfur-containing heterocyclic compounds, it was found that 11-(3-dimethylaminopropyl)-5a,6,7,8,9,10,10a,11-octahydrobenzo[*b*]cyclohepta[*e*][1,4]thiazine (**1f**) had some antihistamine activity without any appreciable effect on the CNS. This finding appears of interest considering the analogy of the cycloalkylbenzothiazine system present in **1f** and that of phenothiazine. Some aminoalkyl derivatives of the latter tricyclic system show both antihistaminic and CNS depressant activities.

We have therefore extended our work to the synthesis of a number of octahydrobenzo[*b*]cyclohepta[*e*][1,4]thiazines (**1a-g**) (Table I) in order to study the variations of pharmacological activity related to reduction and homologation of one of the aromatic rings of phenothiazine. For the few benzo[*b*]cycloalkyl[1,4]thiazine derivatives (tetra- and hexahydrophenothiazines[1-4]) to be found in the literature. only limited pharmacological data have been described.[2]

Chemistry. The 11-(dialkylaminoalkyl)-5a,6,7,8,9,10,10a,11-octahydrobenzo[*b*]cyclohepta[*e*][1,4]thiazines (**1a-g**) (Table I) were prepared by alkylating **1** (R = H) with suitable dialkylaminoalkyl chlorides in boiling xylene in the presence of NaH. Requisite **1** (R = H) was prepared by $NaBH_4$ reduction of the 5a,6,7,8,9,10-hexahydrobenzo[*b*]cyclohepta[*e*][1,4]thiazine obtained as previously reported.[5,6]



1

Pharmacology. The *in vitro* anti-5-hydroxytryptamine (anti-5-HT), antihistamine, and antiacetylcholine activity as well as the effect *in vivo* on the CNS was studied as described in the Experimental Section. Compounds **1a-g** were used as hydrochlorides.

Results

The results of *in vitro* testing for anti 5-HT, antihistamine, and antiacetylcholine are reported in Table II. It can be seen that all test compounds had anti-5-HT activity (Table II) of the same degree (compounds **1b-d,g**) or even superior (compounds **1a,e,f**) to that of the well-known anti-5-HT agent methergoline.[7-9]

Antihistaminic activity was very modest, about 50–200 times less than that of the standard. As was to be expected, compounds **1a-c** containing the dialkylaminoalkyl group in position 11 were more effective than the remaining substances. The test compounds had low antiacetylcholine effects. They were about 50–100 times less potent than atropine. Compounds **1a,b,d** produced a slight depressant effect on the pull-up test at doses of 260, 120, and 175 mg/kg, respectively, and reduced the rotarod performance at concentrations of 300, 125, and 250 mg/kg, respectively, while chlorpheniramine, used as standard, was effective at 18 (pull-up test) and ~100 mg/kg (rotarod performance test). These data suggest a modest interference with coordination of motor activity and muscle tone. All the other substances were devoid of overt effects on the CNS. The substances failed to antagonize reserpine, to potentiate barbiturate effects, and to modify the spontaneous motor activity.

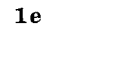
Experimental Section

Chemistry. A mixture of 0.01 mol of **1** (R = H)[5,6] and 0.05 mol of NaH was refluxed in anhydrous xylene (40 ml) for 90 min. A solution of the suitable alkyl chloride (0.04 mol) in anhydrous xylene (30 ml) was added dropwise to this suspension in 2 hr (more volatile alkyl chlorides were added during a longer time). After the addition was completed, the reaction mixture was refluxed for a further 5 hr, cooled, and poured into ice-H_2O, the organic layer was separated, and the aqueous portion was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was distilled under vacuum.

Compounds **1a-g** were dissolved in anhydrous Et_2O and the solution was treated with dry HCl until complete precipitation of

* This paper is dedicated with gratitude to my former professor, Alfred Burger.

Table I. 5a,6,7,8,9,10,10a,11-Octahydrobenzo[*b*]cyclohepta[*e*][1,4]thiazine Derivatives (**1**)

Compd	R	Bp, °C (mm)	Formula[a]	Hydrochloride mp,[b] °C	Formula[a]
1a	$-(CH_2)_2NMe_2$	120–123 (0.05)	$C_{17}H_{26}N_2S$	205–206	$C_{17}H_{27}ClN_2S$
1b	$-(CH_2)_2NEt_2$	120–122 (0.1)	$C_{19}H_{30}N_2S$	178–179	$C_{19}H_{31}ClN_2S$
1c	$-(CH_2)_2$-c-NC_4H_8	120–122 (0.05)	$C_{19}H_{28}N_2S$	175–176	$C_{19}H_{29}ClN_2S$
1d	$-(CH_2)_2$-c-NC_5H_{10}	170–173 (0.05)	$C_{20}H_{30}N_2S$	200–201	$C_{20}H_{31}ClN_2S$
1e		145–148 (0.03)	$C_{20}H_{30}N_2S$	238–239	$C_{20}H_{31}ClN_2S$
1f	$-(CH_2)_3NMe_2$	105–108 (0.01)	$C_{18}H_{28}N_2S$	161–162	$C_{18}H_{30}Cl_2N_2S$
1g	$-(CH_2)_3$-c-NC_5H_{10}	120–122 (0.03)	$C_{21}H_{32}N_2S$	180–181[c]	$C_{21}H_{33}ClN_2S$

[a]Analytical results obtained for C, H, N, and S were within ±0.4% of the theoretical values. [b]Melting points were taken on a Kofler apparatus and are uncorrected. [c]Dried under vacuum at 110° for 70 hr.

Table II. *In Vitro* Inhibitory Activity

Compd	Antiserotonin ID_{50}, g/ml × 10^{-6} (fiducial limits)	Antihistamine ID_{50}, g/ml × 10^{-7} (fiducial limits)	Antiacetylcholine ID_{50}, g/ml × 10^{-7} (fiducial limits)
1a	1.55 (0.32–2.77)	8.0 (1.31–14.69)	5.8 (0.95–10.64)
1b	1.76 (1.55–1.97)	7.9 (5.36–10.44)	5.2 (4.28–6.12)
1c	2.49 (1.59–3.39)	5.7 (1.55–9.95)	6 (4.85–7.15)
1d	1.75 (1.17–2.33)	15.4 (12.86–17.94)	8.9 (3.59–14.20)
1e	1.66 (0.12–3.24)	11.4 (7.48–15.32)	7.3 (0.15–14.45)
1f	1.49 (0.45–2.53)	13.8 (5.73–21.87)	9.8 (1.73–17.87)
1g	2.7 (1.94–3.46)	21.6 (15.37–27.82)	6.4 (5.01–7.78)
Methergoline	2.8 (1.6–4.0)		
Chlorpheniramine		0.11 (0.04–0.18)	
Atropine			0.1 (0.07–0.13)

the salt occurred. After being washed several times with Et_2O the very hygroscopic precipitate was pulverized, dried ($CaCl_2$), and finally crystallized from anhydrous EtOH.

Pharmacology. Methods. (a) *In Vitro* **Experiments.** The experiments were carried out on the isolated guinea pig ileum and rat duodenum, according to the methods described by Magnus[10] and Cahen, *et al.*[11] Anti-5-HT activity was determined on the guinea pig ileum suspended in Kreb's solution containing 1°/oo glucose at 37°. Antihistamine activity was checked on the guinea pig ileum suspended in Tyrode's solution at 37°. Antiacetylcholine activity was studied on the rat duodenum incubated at 38° in Tyrode's solution, containing 1°/oo glucose. All the nutrient solutions were saturated with a mixture of 95% O_2 and 5% CO_2. 5-HT (0.5 μg/ml), histamine (0.1 μg/ml), and acetylcholine (0.1 μg/ml) were employed as spasmogens. Methergoline, chlorpheniramine, and atropine were used as standard. For all the tested substances ID_{50} (the dose which produced a 50% reduction in size of the contraction elicited by a fixed dose of the agonist) and its fiducial limits were determined, according to the method of Steel and Torrie.[12]

(b) *In Vivo* **Experiments.** CNS effects were studied in male albino Blasich mice, used in groups of ten animals, and the following tests, generally indicated as "neurological involvement tests" were performed: pull-up reflex test,[13] modified Thompson's inclined screen test,[14] rotarod performance,[15] righting reflex,[16] and pineal and corneal reflex.[17] Moreover, the antireserpine activity,[18] the potentiation of barbiturate sleeping time,[19] and the spontaneous motor activity were studied according to the literature methods. In the neurological involvement tests compounds **1a–g** were administered in doses ranging from 30 to 300 mg/kg, while the reference substance, chlorpheniramine, was employed at 10–100 mg/kg.

Potentiation of barbiturate sleeping time was determined after oral administration of different doses of the tested substances followed by an ip subhypnotic dose of sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate. Spontaneous motility was studied in an Animex S model apparatus.† All the drugs were administered orally in a fixed volume of 2 ml/100 g of body weight. Reserpine antagonism[18] was tested after ip administration of reserpine in mice ip pretreated with our compounds.

† The Animex S model apparatus is the one produced A. B. Farad, Inc., Hagersten, Sweden.

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A Procedure for Preparing ^{3}H-Labeled Tertiary Amines. Synthesis of [^{3}H]-6,14-*endo*-Etheno-6,7,8,14-tetrahydrooripavine Derivatives

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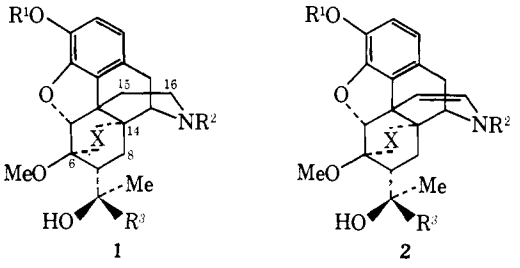
During radiosynthesis it is of paramount importance that the label is introduced at as late a stage as possible. The concept of a synthesis based on the unlabeled required product as starting material is very attractive; techniques such as the Wilzbach gas exposure method[1] and base-catalyzed exchange of aromatic protons[2] illustrate this approach. Both of these methods, however, suffer from distinct disadvantages, the former in that the labeling is unspecific and the latter in that exchange labeled material is susceptible to loss of activity by the reverse exchange process.

In the course of the study of the metabolism of the series of oripavine analgesics **1**, it has been necessary to develop methods of labeling these compounds with tritium. Initially, etorphine (**1a**), a very potent analgesic used for immobilization of animals,[3] was labeled at C-8 by a long inefficient route.[4] We here report a method of introducing a tritium label at carbon atoms α and/or β to a tertiary nitrogen by dehydrogenation to the enamine (*e.g.*, **2**) into which tritium is readily exchanged. The labeled tertiary base is regenerated by subsequent reduction with or without further tritiation.† Use of such a route has the advantages of high specific activity and cheapness inherent in exchange reactions, together with the regiospecificity and stability required for biological studies. Recently, Portoghese[6] has described a somewhat analogous method of labeling secondary amines in the α position by utilizing the acidity conferred on the α protons by the introduction of an *N*-nitroso function.



1

2

	R^1	R^2	R^3	X
a	H	Me	*n*-Pr	-CH=CH-
b	H	$CH_2CH{=}CH_2$	*n*-Pr	-CH=CH-
c	H	CH_2-c-C_3H_5	Me	$-CH_2CH_2-$
d[a]	Me	CH_2-c-C_3H_5	Et	-CH=CH-
e	H	CH_2-c-C_3H_5	Bu	$-CH_2CH_2-$

[a]Thebaine derivative.

†We have previously reported brief details of the synthesis of [15-^{3}H]etorphine from the 15,16-didehydro compound **2a**.[5]

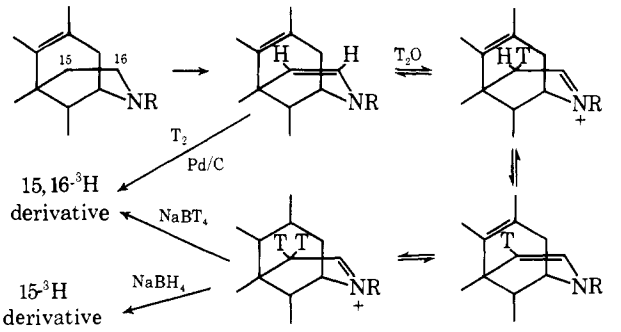
Table I. Specific Activities of Labeled Oripavine Derivatives

Labeling method	Compd	Product	Sp act., mCi/mmol
(i) T_2O (*ca.* 20 Ci) (ii) $NaBH_4$	**1a**	15-^{3}H	100, 220, 260
	1b	15-^{3}H	160
	1c	15-^{3}H	110
	1d	15-^{3}H	26[a]
	1e	15-^{3}H	230
(i) T_2O (*ca.* 20 Ci) (ii) $NaBT_4$ (250 mCi)	**1a**	15,16-^{3}H	900
	1e	15,16-^{3}H	1300
T_2 (*ca.* 10 Ci); Pd/C (10%)	**1a**	15,16-^{3}H	1500, 3600[b]

[a]T_2O used for this reaction was recovered from a previous experiment. [b]After isotope dilution.

The enamines **2**, prepared by the dehydrogenation of the parent tertiary bases **1** with mercury(II) acetate,[5,7] are strong bases and the proton at C-15 equilibrates rapidly with water. Nmr studies with **2e** showed that in $CDCl_3$ the AB quartet (δ 4.26 and 5.93, J = 8 Hz) due to H-15 and H-16 collapsed to a singlet (δ 5.95) on addition of D_2O. Thus, treatment of 15,16-didehydroetorphine (**2a**) with ^3H_2O yielded the enamine specifically labeled at C-15. Subsequent reduction of the iminium salt with $NaBH_4$ yielded [15-^{3}H]etorphine. If the reduction step is carried out in the presence of ^3H_2O, the resulting product contains, in theory, two labeled atoms at C-15 (Scheme I). Other tritiated compounds in the series have been synthesized in this way. The use of NaB^3H_4 yielded 15,16-^{3}H derivatives which showed increased specific activity (Table I).

Scheme I



Etorphine was also labeled in the 15 and 16 positions by hydrogenation of the enamine double bond with $^3H_2$ gas, using 10% palladized charcoal as catalyst; the 6,14-etheno bridge is not reduced under these conditions.[8] The labeled etorphine produced by this route had a higher specific activity than the products of the previous experiments (Table I).

The limiting value for the specific activity of the product in the hydrogenation route is 58 Ci/mmol and though such activities would be difficult to obtain in practice it is apparent that the latter approach is the method of choice in view of the high pharmacological activity of the series and the consequent need for high specific activity.‡ It may not, however, be applicable to compounds containing

‡It would be possible, in fact, to increase further the activity of the hydrogenation product by preliminary equilibration of the enamine with tritiated water to yield, after reduction, a triply labeled product.