ketone had occurred. This was analyzed as the methiodide salt (*vide infra*).

[(3-Methyl-4-oxocyclopentyl)methyl]trimethylammonium Iodide (2). To a solution of 30 mg (0.19 mmol) of the ketoamine mixture in 1 ml of ether was added 100 mg (0.77 mmol) of methyl iodide. The solution was allowed to sit overnight for complete precipitation of the iodide salt. The ether was then decanted and the iodide washed with additional ether to afford 48 mg (87%) of the keto iodide **2**: mp 210–215°; ir (KBr) 3.29, 3.36, 3.39, 3.46, 5.73, 6.71, 6.85, 8.58, 8.73, 9.09, 10.31, and 11.11 μ; nmr (D_2O–external TMS) δ 3.55 (d, 2 H, J = 6 Hz, CH_2N^+), 3.15 (s, 9 H, $^+N(CH_3)_3$), 3.1–2.3 (m, 6 H), and 1.05 (d, 3 H, J = 6 Hz, CH_3CH). Tlc analysis on Silicar plates using 25% acetone–75% methanol (R_f 0.55) and 66% 1-butanol–34% acetic acid (R_f 0.20) as well as other combinations showed only one spot. *Anal.* C, H, N.

Ruthenium Tetroxide Oxidation of the Trimethylammonium Salt 1. To 175 mg (0.585 mmol) of the iodide salt **1** in 0.5 ml of water was added 90 mg (0.6 mmol) of AgCl and the mixture was stirred for 45 min. The AgCl was replaced by the yellow AgI which was removed by filtration and washed with water until the filtrate amounted to 1.0–1.5 ml. To this was added 0.3 ml of 2% $RuCl_3$ followed by 0.84 ml of a 1.42 *N* NaOCl solution (household bleach) in portions while observing the black-yellow-black color change after each addition as the oxidation proceeded. After addition was complete a small amount of 2-propanol was added to ensure complete formation of RuO_2 precipitate. The RuO_2 was then removed by filtration and the water removed *in vacuo* to give the keto chloride product and sodium chloride. The keto chloride was dissolved in acetone and an acetone solution of 88 mg (0.59 mmol) of NaI was added to afford the keto ammonium iodide **2** which was recrystallized from acetone–hexane giving 136 mg (0.46 mmol, 79%) of the iodide salt; the melting point, ir, nmr, and tlc results were identical with those previously given (*vide supra*). This route was chosen for synthesis of material used in subsequent biological studies because of the better overall yield and less number of steps.

Animal Tissue Tests. A. Guinea Pig Ileum. The tissue tests consisted of *in vitro* studies on whole guinea pig ileum preparations obtained from male American Standard guinea pigs, small stock. Four preparations immersed in Tyrode solution at 37° were used at each dose level. All compounds tested gave nearly full contraction indicating unit intrinsic activity. Typical dose–response curves were obtained with the concentration at peak half-height being used for relative biological activity. The results are given in Table I. All tests were conducted on racemic material.

B. Chicken Biventor Muscle. The method employed for nicotinic activity of ±-**2** is fully detailed in ref 7.

Acknowledgments. This work was supported by NIH Grant GM16611 and by the University of Kansas General Research Fund. The technical assistance of John Dickerson and Janet Kongs, helpful discussions with Drs. R. A. Wiley and R. G. Carlson, and the biological testing by Professor E. J. Walaszek at the University of Kansas Medical Center are gratefully acknowledged. We also wish to acknowledge Professor P. G. Waser (Zurich University) for confirming the muscarinic and nicotinic activity for **1** and **2** on other preparations. The results will appear later in a full paper on the pharmacology of the desethermuscarines.

References

(1) K. G. R. Sundelin, R. A. Wiley, R. S. Givens, and D. R. Rademacher, *J. Med. Chem.*, **16**, 235 (1973).
(2) Presented at the 165th National Meeting of the American Chemical Society, Dallas, Texas, April 8–13, 1973, Abstract MEDI 031.
(3) D. J. Triggle, "Neurotransmitter-Receptor Interactions," Academic Press, New York, N. Y., 1971, pp 259–260.
(4) S. Wolfe, S. K. Hasan, and J. R. Campbell, *Chem. Commun.*, 1420 (1970).
(5) J. J. Partridge, N. K. Chadha, and M. R. Usbokovic, *J. Amer. Chem. Soc.*, **95**, 532 (1973).
(6) Reference 3, p 254.
(7) "Pharmacological Experiments of Isolated Preparations," Department of Pharmacology, University of Edinburgh, E. S. Livingston, Ltd., Edinburgh, 1968, pp 54 ff.

Synthesis and Central Nervous System Activity of 1,2,3,4-Tetrahydro-1-amino-4-phenylnaphthalenes

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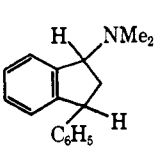
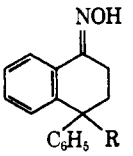
The reported analgetic activity of 1-dimethylamino-3-phenylindan (**1**)[1,†] prompted the synthesis, from 4-cyano-4,4-diphenylbutyric acid,[3] of the compounds described in Table I. The reductive decyanation of this acid with sodium and ethanol gave 4,4-diphenylbutyric acid which was cyclized to 3,4-dihydro-4-phenyl-1(2*H*)-naphthalenone.[4]



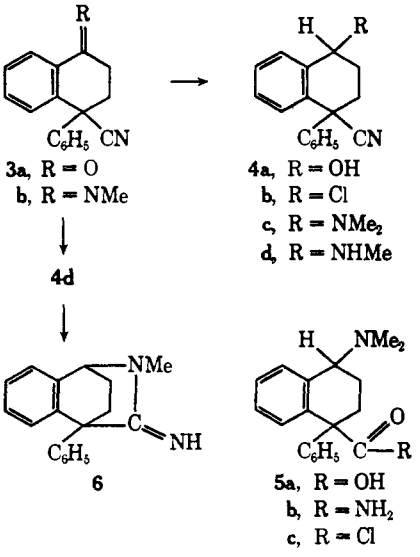
1



2a, R = H
b, R = CN

The oxime **2a** of this ketone, reduced with Raney nickel, gave compounds **13** and **14** (Table I) and these amines were converted to compounds **15–18** and **22–25** by known procedures. This scheme failed with the cyanooxime **2b**. Its reduction by a Zn–AcOH procedure[5] gave a complex mixture containing 50–60% of the isomeric cyanoamines from which only **27** was isolated in low yield. The reduction of **2b** with Raney nickel in $(AcO)_2O$ gave a mixture of the acetaminonitriles **28** and **29** which was not easily separated. Since the acetyl group of neither isomer could be hydrolyzed by either acid or base without converting the cyano group to an amide, this approach was replaced by that shown in Scheme I.

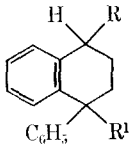
Scheme I



In Scheme I the $NaBH_4$ reduction of **3a**‡ gave a mixture of the cis and trans cyano alcohols **4a**, which with $SOCl_2$ yielded a similar mixture of the cyano chlorides **4b**. The separation of the **4b** isomers was not attempted since the difference in their rate of reaction with Me_2NH in PhMe enabled the preparation of the pure *cis*- and *trans*-aminonitriles **4c**. Their subsequent conversion to the cor-

† See also ref 2 for a brief review of the literature on this compound.
‡ Compound subsequently described; see ref 6.

Table I. 1,2,3,4-Tetrahydro-1-amino-4-phenylnaphthalenes and Intermediates



No.	R	R¹	Config[a]	Mp or bp (mm), °C	Crystn solvent	Yield, %	Formula	Analyses	CNS activity in mice Adm[b]	Stim[c]	Depr[d]	Ld[e]
13	NH_2	H	x	59–61	EtOH	93[f]	$C_{16}H_{17}N$	C, H, N				
13a	$NH_2 \cdot HCl$	H	x	303–305	EtOH		$C_{16}H_{18}ClN$	C, H, N	po	11		120
14	NH_2	H	y	135 (1)		93[f]	$C_{16}H_{17}N$	C, H, N				
14a	$NH_2 \cdot HCl$	H	y	275–278	EtOH		$C_{16}H_{18}ClN$	C, H, N	po	36		400
15	NH(COMe)	H	x	171–172	MeCN		$C_{18}H_{19}NO$	C, H, N	ip		10	>1000
16	NH(COMe)	H	y	193–194	EtOH		$C_{18}H_{19}NO$	C, H, N	ip		10	>1000
17	NH(COOEt)	H	x	132–135	*i*-Pr_2O	85[g]	$C_{19}H_{21}NO_2$	C, H, N	po		120	>400
18	NH(COOEt)	H	y	111–114	*i*-Pr_2O	79[g]	$C_{19}H_{21}NO_2$	C, H, N	po		120	>400
19	CN	H	x	105–107	MeCN	94[h]	$C_{17}H_{15}N$	C, H, N				
20	$CONH_2$	H	x	179–181	MeCN	91	$C_{17}H_{17}NO$					
21	NH(COOMe)	H	x	119–120	MeOH	84[i]	$C_{18}H_{19}NO_2$	C, H, N				
22	NHMe·HCl	H	x	223–225	EtOH	73[j]	$C_{17}H_{20}ClN$	C, H, N	po	36		120
23	NHMe·HCl	H	y	233–235	EtOH	78[j]	$C_{17}H_{20}ClN$	C, H, N	po		36	400
24	NMe_2	H	x	88–90	Hexane	89[k]	$C_{18}H_{21}N$	C, H, N				
24a	$NMe_2 \cdot HCl$	H	x	225–228	EtOH–Et_2O		$C_{18}H_{22}ClN$	C, H, N	ip	30		100
25	NMe_2	H	y	61–63	Hexane	87[k]	$C_{18}H_{21}N$	C, H, N				
25a	$NMe_2 \cdot M$	H	y	149–150	EtOH–H_2O		$C_{22}H_{25}NO_4$	C, H, N	po	30	300	>300
26	Cl	CN[m]		80–83	EtOH	31	$C_{17}H_{14}ClN$	Cl, C, H, N				
27	NH_2	CN[n]	y	138–140	Hexane		$C_{17}H_{16}N_2$	C, H, N				
27a	$NH_2 \cdot HCl$	CN	y	274–276	H_2O		$C_{17}H_{17}ClN_2$	C, H				
28	NH(COMe)	CN[n]	x	204–206	C_6H_6	19[p]	$C_{19}H_{18}N_2O$	C, H				
29	NH(COMe)	CN[q]	y	201–203	C_6H_6		$C_{19}H_{18}N_2O$	C, H				
30	NHMe·HCl	CN	x	225–227	EtOH	20	$C_{18}H_{18}ClN_2$	C, H, N	po	30		300
31	NHMe·M[l]	CN	y	180–181	EtOH–EtOAc	24	$C_{22}H_{22}N_2O_4$	C, H, N	po	30		>300
32	NHMe	$CONH_2$[r]	y	123–124	Et_2O	46	$C_{18}H_{20}N_2O$	C, H, N				
32a	NHMe·HCl	$CONH_2$	y	278–280	EtOH		$C_{18}H_{21}ClN_2O$	C, H, N	po		300	>300
33	NMe_2	CN	y	81–82	MeOH		$C_{19}H_{20}N_2$	C, H				
33a	$NMe_2 \cdot HCl$	CN	y	246–247	EtOH		$C_{19}H_{21}ClN_2$	C, H	ip	100	30	300
34	NMe_2	CN	x	120–122	MeOH		$C_{19}H_{20}N_2$	C, H				
34a	$NMe_2 \cdot HCl$	CN	x	212–214	*i*-PrOH		$C_{19}H_{21}ClN_2$	C, H	ip	30		100
35	NMe_2	$CONH_2$[s]	x	174–176	*i*-PrOH	81	$C_{19}H_{22}N_2O$					
35a	$NMe_2 \cdot M$	$CONH_2$	x	161–163	EtCOMe		$C_{23}H_{26}N_2O_5$	C, H	ip		30	300
36	NMe_2	$CONH_2$[s]	y	166–168	EtCOMe	96	$C_{19}H_{22}N_2O$	C, H				
36a	$NMe_2 \cdot HCl$	$CONH_2$	y	247–249	EtOH		$C_{19}H_{23}ClN_2O$	C, H	ip		3	300
37	NMe_2	CONH(Me)[t]	y	152–155	*i*-PrOAc	41	$C_{20}H_{24}N_2O$	C, H, N				
37a	$NMe_2 \cdot HCl$	CONH(Me)	y	214–216	*i*-PrOH		$C_{20}H_{25}ClN_2O$	C, H, N	po		120	400
38	NMe_2	$CON(Me)_2$[t]	y	131–132	*i*-PrOAc	84	$C_{21}H_{26}N_2O$	C, H				

38a	$NMe_2 \cdot HCl$	$CON(Me)_2$	y	85–110	H_2O		$C_{21}H_{27}ClN_2O \cdot 2H_2O$	C, H, N	po	3	30	100
39	NMe_2	$CON(Me)_2$[t]	x	127–129	*i*-PrOAc	35	$C_{21}H_{26}N_2O$	C, H				
39a	$NMe_2 \cdot HCl$	$CON(Me)_2$	x	256–258	EtOH–Et_2O		$C_{21}H_{27}ClN_2O$	C, H	ip	10		300
40	$NMe_2 \cdot H_2SO_4$	COOH[u]	y	181–184	H_2O	86	$C_{19}H_{23}NO_6S \cdot H_2O$	C, H				
41	$NMe_2 \cdot H_2SO_4$	COOH[u]	x	110 dec	EtOH	77	$C_{19}H_{23}NO_6S \cdot 2H_2O$	C, H, N				
42	NMe_2	COOMe	y	91–93	Hexane	83	$C_{20}H_{23}NO_2$	C, H, N				
42a	$NMe_2 \cdot HCl$	COOMe	y	224–225	MeOH		$C_{20}H_{24}ClNO_2$	C, H, N	ip		3	300
43	NMe_2	COOMe	x	111–113	Hexane	89	$C_{20}H_{23}NO_2$	C, H, N				
43a	$NMe_2 \cdot HCl$	COOMe	x	191–193	EtOAc		$C_{20}H_{24}ClNO_2$	C, H	ip		30	100
44	NMe_2	CO(Et)[v]	x	110–112	Hexane	26	$C_{21}H_{25}NO$	C, H, N				
44a	$NMe_2 \cdot HCl$	CO(Et)	x	238–239.5	EtOH		$C_{21}H_{26}ClNO$	H, N; C[w]	ip		100	>100

[a] x denotes isomer with C_6H_5 trans to R; y, isomer with these groups cis. [b] Route of administration; doses given in mg/kg calculated as free base. [c] Minimum dose at which behavioral stimulation was observed. [d] Minimum dose at which behavioral depression was observed. [e] Dose causing deaths. [f] Combined yield of **13** and **14**. [g] Prepared from the amine and EtOOCCl in pyridine at 5°. [h] Prepared from **20** and TsCl in pyridine. [i] Prepared from **20** with Br_2 and NaOMe in MeOH. [j] Prepared by $LiAlH_4$ reduction of the corresponding carbamate. [k] From HCHO·HCOOH and the corresponding primary amine. [l] M maleate. [m] Configuration unknown. [n] Prepared from **2a** by the procedure in ref 5. [o] By hydrogenation of **2a** with Raney Ni in $(CH_3CO)_2O$ at 50°. [p] Amount isolated pure. [q] Acetylation of **27**. [r] From the corresponding nitrile and concentrated H_2SO_4, 1 hr at 60°. All efforts to prepare the x isomer from **30** gave 1,4-ethano-2-methyl-4-phenyl-1,2,3,4-tetrahydro-3-quinolone [G. Walker and D. Alkalay, *J. Org. Chem.*, **32**, 2213 (1967)]. [s] From the corresponding nitrile and 90% H_2SO_4, 4 hr at 96°. [t] From the amine and acid chloride in ether. [u] From the corresponding nitrile refluxed 6 hr in aqueous H_2SO_4, bp 145–150°. [v] From **34** and EtMgBr, procedure in the office of the Publication Board, Department of Commerce Report PB 981, p 96A. [w] C: calcd, 73.34; found, 72.87.

responding acids **5a** and amides **5b** was uneventful, but a preparation of the acid chlorides **5c** gave the unexpected reactions shown in Scheme II.

Scheme II

A moist cake of the sulfate of each isomer of **5a** containing some H_2SO_4 gave with $SOCl_2$ at 25° almost exclusively the decarboxylated compounds **9** and **10**. Possibly these compounds were formed *via* the mixed anhydride **7** which gave **9** directly or which decomposed to **8** and the latter was sulfonated to **9**. Thionyl chloride is a good solvent for sulfonations§ and may have converted **9** to the sulfone **10**, although one attempt to effect this conversion with pure **9** failed. Compounds **9** and **10** were unstable as free bases and eliminated Me_2NH, giving **11** and **12**, respectively. The sulfone **12** was identical with a sample of this compound prepared by another procedure.[9]

The desired acid chlorides **5c** subsequently were made from purified **5a** sulfates with excess $SOCl_2$ kept below 0° during the reaction and removal of the excess reactant or by the use of oxalyl chloride.

The configurations of the isomers of **4c** and consequently that of their derivatives were established by the conversion **3a** → **3b** → **4d** → **6** in Scheme I. The $NaBH_4$ reduction of **3b** gave both isomers of **4d**. Their hydrochlorides were separated and the isomer with *cis*-cyano and methylamino groups cyclized to the amidine **6** at its melting point. Each form of **4d** was methylated with formic acid and formaldehyde to the corresponding **4c**.

The configurations of compounds **13–25** were tentatively assigned as follows. A mixture of the isomeric 1,2,3,4-tetrahydro-4-phenyl-1-naphthonitriles from the monodecyanation of the corresponding 1,4-dinitriles[10,11] was hydrolyzed and equilibrated in refluxing alkali to a mixture of the isomeric carboxamides. The major product, **20**, assigned the trans diequatorial configuration, gave with bro-

§ This work has not been published; private communication from Professor J. Bradley.[7] Reference 8 gives a brief summary of this work.

mine and sodium methylate in methanol the methyl homolog 21 of compound 17. The $LiAlH_4$ reduction of 17 and of 21 gave 22 and the configurations of the other compounds were related to it. Trans 1,4 groups in tetralins are not completely diequatorial and this assignment is tentative, but, in agreement, *trans*-tetralin-1,4-dicarboxylic acid was found the most stable form.[12]

The dimethylaminonitriles 33 and 34 were decyanated with sodamide in toluene and gave predominately 24 and 25, respectively. Thus, inversion occurred in each instance.

Pharmacology. The compounds were studied under the direction of Dr. Samuel Irwin in the Pharmacology Department of the Schering Corp. The screening procedure was the comprehensive behavioral, neurologic, and autonomic evaluation of Irwin.[13] Analgesia was measured by the response to a pinching of the tail with a forceps. In this screen (doses in mg/kg) morphine sulfate at 10 intraperitoneally or 30 orally produced 50% of the maximum analgetic response. Perphenazine was a behavioral depressant at 0.3 intraperitoneally, at 1 orally; and *d*-amphetamine was a stimulant at 1 intraperitoneally and at 1-3 orally.

Groups of three male CF No. 1S mice were treated orally or intraperitoneally with varying dosage schedules of the compounds and the data are summarized in Table I. With most pairs of the isomeric amines (**13a**, **14a**; **22**, **23**; **33a**, **34a**; **35a**, **36a**; **42a**, **43a**) the isomers with the x configuration were more behaviorally active as stimulants and were more toxic than their y counterparts; the latter were more active as depressants. Though not administered by the same route, **38a** and **39a**, which possess a bulky functional group at position 4, are an apparent exception. Also screened in mice (doses in mg/kg orally) was **6**·HCl, a depressant at 100, lethal at 300; **9**, a behavioral stimulant at 100, lethal at 300; and **10**·HCl, a behavioral stimulant at 10, lethal >100. Only **36a** and **42a** showed any analgetic action and this only at doses 30 and 10 times greater, respectively, than those producing depression.

Experimental Section

Melting points were taken in open capillary tubes with a Hershberg apparatus and are uncorrected. Where analyses are indicated only by the symbols of the elements, analytical results were within ±0.4% of the theoretical values.

4,4-Diphenylbutyric Acid. The salt prepared from 132.5 g (0.5 mol) of 4-cyano-4,4-diphenylbutyric acid and 0.5 mol of NaOEt in 400 ml of EtOH was heated to reflux in a mantle in a 5 l., three-neck flask bearing an efficient wide-bore condenser, blade stirrer, and addition funnel. Without further heating, 161 g (7 mol) of Na was added through the condenser in 10-20-g chunks as rapidly as the vigorous frothing and refluxing allowed. The mixture was stirred slowly to avoid disintegrating the molten lumps. As the addition proceeded the mixture thickened, heating was begun, and 1.2 l. of EtOH was added at a rate just sufficient to keep the Na free of a coating. Heating was continued until all of the Na had dissolved. The condenser was arranged for distillation and 1.2 l. of H_2O was added slowly to the hot mixture and most of the EtOH distilled. The cooled residue was extracted with 500 ml of PhH and the extract was washed with 500 ml of H_2O. This aqueous wash plus the basic solution was cooled in ice and acidified to pH 3 with 20% HCl in a well-ventilated hood. (Caution, HCN is evolved.) The product crystallized on cooling and was filtered, washed with H_2O, and dissolved in 1.5 l. of warm PhH. This solution was washed with 2 × 200 ml of H_2O, and distillation left 104-114 g (87-95%) of cyano-free acid, mp 104-108°, which was suitable for use. Crystallization from MeCN, 2 ml/g, gave acid, mp 108-110°.

1,2,3,4-Tetrahydro-1-amino-4-phenylnaphthalenes (13 and 14). The oxime **2a** (95 g), hydrogenated at 100° in 900 ml of NH_3 saturated EtOH with Raney nickel and H_2 at 60 kg/cm², gave 77 g of a distilled mixture of the amines. Dry HCl was added to this mixture in 400 ml of EtOH and the salt was collected. Three recrystallizations from 70% EtOH gave 21 g of **13a**, mp 290-300°. The base recovered from the first two crystalline liquids was acetylated and crystallized from MeOH: yield, 30 g of amide **16**. This compound was hydrolyzed to **14a** with HCl.

1,2,3,4-Tetrahydro-4-cyano-1-dimethylamino-4-phenylnaphthalenes (33 and 34). To a stirred suspension of 98.8 g (0.4 mol) of powdered ketone **3a** in 2 l. of MeOH 12.5 g (0.33 mol) of $NaBH_4$ was added in small portions at 5-10° over 2 hr. After 4 hr at 20° the MeOH was distilled and the product was extracted with C_6H_6 and H_2O. The solution was concentrated and the carbonyl-free oil in 100 ml of PhH was added to 150 ml of $SOCl_2$ and refluxed for 10 min. The mixture was concentrated *in vacuo*; 150 ml of PhH was added and removed *in vacuo*. The residue in 150 ml of PhMe was added at −10° to 250 ml of liquid Me_2NH and the mixture was sealed in a pressure bottle and kept at 25° for 4 days. The excess Me_2NH was distilled and the PhMe was washed with H_2O and extracted with 5% HCl. Basification of the acid extracts gave 51 g of **34**, mp 108-115°. The PhMe solution was concentrated *in vacuo* and triturated with hexane: yield, 33 g of the chloronitrile **26**. This compound in 400 ml of MeOH was saturated with Me_2NH at 0°, sealed in a pressure bottle, and kept with an occasional shaking at 25° for 5 days. The usual work-up gave 23 g of **33**.

1,2,3,4-Tetrahydro-4-cyano-1-methylamino-4-phenylnaphthalene Salts (30 and 31). The ketone **3a** (80 g) was stirred in a bath at 150° and a rapid stream of $MeNH_2$ was passed through it for 2 hr. Water was removed continuously as distillate and the residue in 900 ml of MeOH was reduced with 16 g of $NaBH_4$ at 5-10°. The products, isolated and separated with 5% HCl in the usual manner, were 30.5 g of the cyano alcohols 4a and a 49.5-g basic fraction whose HCl salt, crystallized from EtOH, gave 19.5 g of **30**. The bases recovered from the crystallization liquid were chromatographed on 1250 g of silica gel powder. The first $CHCl_3$ eluates (monitored by tlc) gave 20 g of a thick oil which was converted to **31**.

1,2-Dihydro-1-dimethylamino-4-phenylnaphthalene-3-sulfonic Acid (9). The wet cake of the hydrated salt 41 from the hydrolysis of 10 g of **34** was added in small portions with stirring to 500 ml of $SOCl_2$ containing 1.5 ml of H_2SO_4. There was a vigorous evolution of gases. After stirring for 3 days the $SOCl_2$ was distilled *in vacuo* (bath below 40°) and 100 ml of cold MeOH was added. When the gum had dissolved the solution was kept at 45° for 3 hr and refluxed for 0.5 hr. The compound was collected and washed: yield, 4.8 g; mp 259-260°. *Anal.* ($C_{18}H_{19}NO_3S$) H, N; C: calcd, 62.22; found, 62.88.

5,6-Dihydro-5-dimethylaminobenzo[*d*]naphtho[2,1-*b*]thiophene 7,7-Dioxide Hydrochloride (10). The MeOH solution from the above preparation was distilled *in vacuo* and the residue was shaken with Et_2O and cold 10% Na_2CO_3. The extract was dried briefly (K_2CO_3), filtered, and treated with dry HCl. The crystals were filtered and recrystallized from EtOH; yield, 2.9 g; shrinking 200°; mp 233-235°. *Anal.* ($C_{18}H_{17}NO_2S$·HCl·H_2O) C, H, N.

Sodium 4-Phenylnaphthalene-3-sulfonate (11). Compound **9** (3 g) was refluxed with 20 ml of 10% NaOH until the evolution of Me_2NH ceased. Concentration and cooling gave hydrated plates which were crystallized from 50% EtOH and dried at 100° in a 2-mm vacuum for 6 hr: mp 312-315°. *Anal.* ($C_{16}H_{11}O_3SNa$) C, H.

Benzo[*d*]naphtho[2,1-*b*]thiophene 7,7-Dioxide (12). The free base from **10** in Et_2O solution rapidly decomposed to **12**: mp 235-236°; identical with authentic **12**[9] and with material prepared from **11** and poly-H_3PO_4 by a published procedure.[14]

1,2,3,4-Tetrahydro-1,4-ethano-3-imino-2-methyl-4-phenylisoquinoline Hydrochloride (6). The salt **15**, kept slightly above its melting point for a few minutes, resolidified and was recrystallized from EtOH: mp 295-297°. *Anal.* ($C_{18}H_{19}ClN_2$) C, H, N.

The free base from this salt and aqueous Na_2CO_3 was crystallized from MeCN: mp 190-192°. *Anal.* ($C_{18}H_{18}N_2$) C, H, N.

1,2,3,4-Tetrahydro-4-carbomethoxy-1-dimethylamino-4-phenylnaphthalene (42). Finely powdered pure sulfate salt **40** (7 g) was added to 200 ml of $SOCl_2$ at 0° and stirred at this temperature until it dissolved, *ca.* 2 hr. The excess $SOCl_2$ was distilled *in vacuo* below 0°, 100 ml of cold MeOH was added all at once to the residue, and it was refluxed for 1 hr. The solution was filtered and evaporated, and the base was recovered in the usual manner.

Excess oxalyl chloride at 25° also was used in this preparation with good results.

1,2,3,4-Tetrahydro-4-phenyl-1-naphthonitriles. A cis/trans mixture of the corresponding 1,4-dinitriles,[10] 103.3 g (0.4 mol), mp 90-110°, and the $NaNH_2$ prepared from 32.2 g (1.4 mol) of Na were refluxed with stirring in 1500 ml of PhMe for 10 hr. The usual work-up gave 71 g of mononitriles: bp 170-173° (1 mm); mp

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.

Acknowledgment. The authors thank Dr. Allen Barnett for the evaluation and summary of the pharmacological data.

References

(1) J. A. Barltrop, R. M. Acheson, P. G. Philpott, K. E. MacPhee, and J. S. Hunt, *J. Chem. Soc.*, 2928 (1956).
(2) R. A. Hardy and M. G. Howell in "Analgetics," G. de Stevens, Ed., Academic Press, New York, N. Y., 1965, p 249.
(3) H. Breitschneider, H. Deutscher, W. Klotzer, and M. Sander, *Monatsh. Chem.*, **89**, 288 (1958).
(4) S. Wawzonek and J. Kozikowski, *J. Amer. Chem. Soc.*, **76**, 1641 (1954).
(5) E. Testa and F. Fava, *Chimia*, 11, 307 (1957).
(6) W. Herz and G. Caple, *J. Org. Chem.*, **29**, 1691 (1964).
(7) J. Bradley, P. Perkins, and J. Polisin, paper presented at the 138th National Meeting of the American Chemical Society, New York, N. Y., Sept 1960.
(8) E. Gilbert, *Synthesis*, 1, 1 (1969).
(9) F. Bordwell, W. McKellin, and D. Babcock, *J. Amer. Chem. Soc.*, **73**, 5566 (1951).
(10) H. Newly and J. Erickson, *J. Amer. Chem. Soc.*, **72**, 5645 (1950).
(11) J. Colonge, J. Dreux, and J. Regeaud, *Bull. Soc. Chim. Fr.*, 1244 (1959).
(12) T. Lyssy, *J. Org. Chem.*, **27**, 5 (1962).
(13) S. Irwin, "Clinical Pharmacological Techniques," J. H. Nodine and P. S. Siegler, Ed., Yearbook Medical Publishers, Chicago, Ill., 1964, Chapter 4.
(14) G. Graybill, *J. Org. Chem.*, 32, 2931 (1967).

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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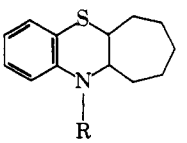
In the course of our earlier studies on sulfur-containing heterocyclic compounds, it was found that 11-(3-dimethylaminopropyl)-5a,6,7,8,9,10,10a,11-octahydrobenzo[*b*]cyclohepta[*e*][1,4]thiazine (**1f**) had some antihistamine activity without any appreciable effect on the CNS. This finding appears 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]



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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.