

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  $\mu$ ; nmr ( $D_2O$ -external TMS)  $\delta$  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 Biventer Muscle.** The method employed for nicotinic activity of  $\pm$ -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 desethersmuscarines.

## References

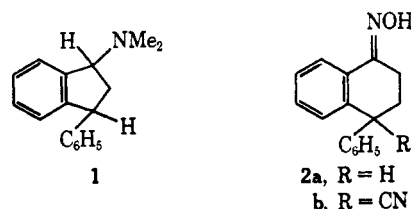
- (1) K. G. R. Sundelin, R. A. Wiley, R. S. Givens, and D. R. Rademacher, *J. Med. Chem.*, **16**, 235 (1973).
- (2) Presented at the 165th National Meeting of the American Chemical Society, Dallas, Texas, April 8–13, 1973, Abstract MEDI 031.
- (3) D. J. Triggle, "Neurotransmitter-Receptor Interactions," 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

Lewis A. Walter,\* Wei K. Chang, Joanne Kenney, and Irina Douvan

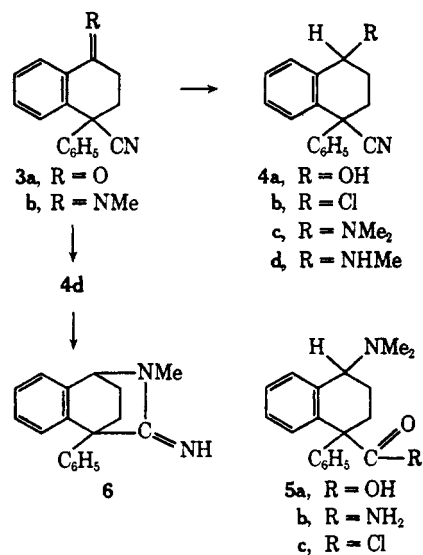
Medicinal Chemistry Research Department, Schering Corporation, Bloomfield, New Jersey 07003. Received October 26, 1973

The reported analgetic activity of 1-dimethylamino-3-phenylnindan (1)<sup>1,†</sup> prompted the synthesis, from 4-cyano-4,4-diphenylbutyric acid,<sup>3</sup> 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(2H)-naphthalenone.<sup>4</sup>



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 cyano oxime 2b. Its reduction by a Zn–AcOH procedure<sup>5</sup> 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



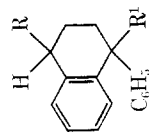
In Scheme I the  $NaBH_4$  reduction of 3a<sup>†</sup> gave a mixture of the *cis* and *trans* cyano alcohols 4a, which with  $SOCl_2$  yielded a similar mixture of the cyano chlorides 4b. The separation of the 4b isomers was not attempted since the difference in their rate of reaction with  $Me_2NH$  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	R <sup>1</sup>	Config <sup>a</sup>	Mp or bp (mm), °C	Crystn solvent	Yield, %	Formula	Analyses	Adm <sup>b</sup>	CNS activity in mice		
										Stim <sup>c</sup>	Depr <sup>d</sup>	Ld <sup>e</sup>
13	NH <sub>2</sub> ·HCl	H	x	59-61	EtOH	93/	C <sub>16</sub> H <sub>17</sub> N	C, H, N	po	11		120
13a	NH <sub>2</sub> ·HCl	H	x	303-305	EtOH	93/	C <sub>16</sub> H <sub>18</sub> ClN	C, H, N	po			
14	NH <sub>2</sub> ·HCl	H	y	135 (1)	EtOH		C <sub>16</sub> H <sub>17</sub> N	C, H, N	po			
14a	NH <sub>2</sub> ·HCl	H	y	275-278	EtOH		C <sub>16</sub> H <sub>18</sub> ClN	C, H, N	ip	36	10	400
15	NH(COMe)	H	x	171-172	MeCN		C <sub>18</sub> H <sub>19</sub> NO	C, H, N	ip			>1000
16	NH(COMe)	H	y	193-194	EtOH		C <sub>18</sub> H <sub>19</sub> NO	C, H, N	ip		10	>1000
17	NH(COOEt)	H	x	132-135	i-Pr <sub>2</sub> O	85 <sup>a</sup>	C <sub>19</sub> H <sub>21</sub> NO <sub>2</sub>	C, H, N	po		120	>400
18	NH(COOEt)	H	y	111-114	i-Pr <sub>2</sub> O	79 <sup>a</sup>	C <sub>19</sub> H <sub>21</sub> NO <sub>2</sub>	C, H, N	po		120	>400
19	CN	H	x	105-107	MeCN	94 <sup>b</sup>	C <sub>17</sub> H <sub>15</sub> N	C, H, N				
20	CONH <sub>2</sub>	H	x	179-181	MeCN	91	C <sub>17</sub> H <sub>17</sub> NO	C, H, N				
21	NH(COOMe)	H	x	119-120	MeOH	84 <sup>c</sup>	C <sub>18</sub> H <sub>19</sub> NO <sub>2</sub>	C, H, N	po			120
22	NHMe·HCl	H	x	223-225	EtOH	73 <sup>d</sup>	C <sub>17</sub> H <sub>20</sub> ClN	C, H, N	po	36	36	400
23	NHMe·HCl	H	y	233-235	EtOH	78 <sup>e</sup>	C <sub>17</sub> H <sub>20</sub> ClN	C, H, N				
24	NMe <sub>2</sub>	H	x	88-90	Hexane	89 <sup>f</sup>	C <sub>18</sub> H <sub>21</sub> N	C, H, N	ip	30		100
24a	NMe <sub>2</sub> ·HCl	H	x	225-228	EtOH-Et <sub>2</sub> O	87 <sup>g</sup>	C <sub>18</sub> H <sub>22</sub> ClN	C, H, N				
25	NMe <sub>2</sub>	H	y	61-63	Hexane		C <sub>18</sub> H <sub>21</sub> N	C, H, N	po			>300
25a	NMe <sub>2</sub> ·M	H	y	149-150	EtOH-H <sub>2</sub> O		C <sub>22</sub> H <sub>25</sub> NO <sub>4</sub>	C, H, N				
26	Cl	CN <sup>m</sup>	y	80-83	EtOH	31	C <sub>17</sub> H <sub>14</sub> ClN	Cl, C, H, N	po	30	300	
27	NH <sub>2</sub>	CN <sup>n</sup>	y	138-140	Hexane		C <sub>17</sub> H <sub>16</sub> N <sub>2</sub>	C, H, N				
27a	NH <sub>2</sub> ·HCl	CN	y	274-276	H <sub>2</sub> O	19 <sup>h</sup>	C <sub>17</sub> H <sub>17</sub> ClN <sub>2</sub>	C, H				
28	NH(COMe)	CN <sup>o</sup>	x	204-206	C <sub>6</sub> H <sub>6</sub>		C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O	C, H				
29	NH(COMe)	CN <sup>q</sup>	y	201-203	C <sub>6</sub> H <sub>6</sub>		C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O	C, H	po	30		300
30	NHMe·HCl	CN	x	225-227	EtOH	20	C <sub>18</sub> H <sub>18</sub> ClN <sub>2</sub>	C, H, N	po	30		>300
31	NHMe·M <sup>t</sup>	CN	y	180-181	EtOH-EtOAc	24	C <sub>22</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	C, H, N	po			
32	NHMe	CONH <sub>2</sub> <sup>r</sup>	y	123-124	Et <sub>2</sub> O	46	C <sub>18</sub> H <sub>20</sub> N <sub>2</sub> O	C, H, N	po		300	>300
32a	NHMe·HCl	CONH <sub>2</sub>	y	278-280	EtOH		C <sub>18</sub> H <sub>21</sub> ClN <sub>2</sub> O	C, H, N				
33	NMe <sub>2</sub>	CN	y	81-82	MeOH		C <sub>19</sub> H <sub>20</sub> N <sub>2</sub>	C, H	po			
33a	NMe <sub>2</sub> ·HCl	CN	y	246-247	EtOH		C <sub>19</sub> H <sub>21</sub> ClN <sub>2</sub>	C, H	ip	100	30	300
34	NMe <sub>2</sub>	CN	x	120-122	MeOH		C <sub>19</sub> H <sub>20</sub> N <sub>2</sub>	C, H	ip			
34a	NMe <sub>2</sub> ·HCl	CN	x	212-214	i-PrOH		C <sub>19</sub> H <sub>21</sub> ClN <sub>2</sub>	C, H	ip	30		100
35	NMe <sub>2</sub>	CONH <sub>2</sub> <sup>s</sup>	x	174-176	i-PrOH	81	C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> O	C, H	ip		30	300
35a	NMe <sub>2</sub> ·M	CONH <sub>2</sub>	x	161-163	EtCOMe		C <sub>23</sub> H <sub>26</sub> N <sub>2</sub> O <sub>5</sub>	C, H	ip			
36	NMe <sub>2</sub>	CONH <sub>2</sub> <sup>s</sup>	y	166-168	EtCOMe	96	C <sub>19</sub> H <sub>22</sub> N <sub>2</sub> O	C, H	ip		3	300
36a	NMe <sub>2</sub> ·HCl	CONH <sub>2</sub>	y	247-249	EtOH		C <sub>19</sub> H <sub>23</sub> ClN <sub>2</sub> O	C, H, N	ip			
37	NMe <sub>2</sub>	CONH(Me) <sup>t</sup>	y	152-155	i-PrOAc	41	C <sub>20</sub> H <sub>24</sub> N <sub>2</sub> O	C, H, N	po		120	400
37a	NMe <sub>2</sub> ·HCl	CONH(Me)	y	214-216	i-PrOH		C <sub>20</sub> H <sub>25</sub> ClN <sub>2</sub> O	C, H, N				
38	NMe <sub>2</sub>	CON(Me) <sub>2</sub> <sup>t</sup>	y	131-132	i-PrOAc	84	C <sub>21</sub> H <sub>26</sub> N <sub>2</sub> O	C, H				

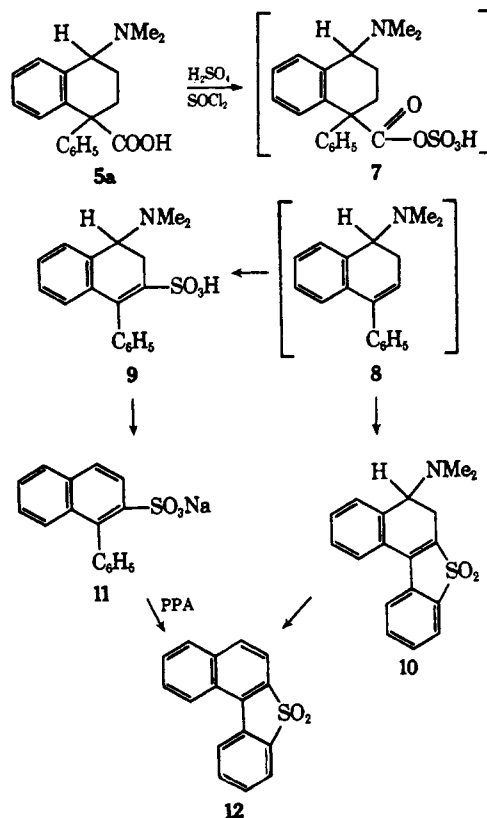


38a	39	39a	40	41	42	42a	43	43a	44	44a
NMe <sub>2</sub> ·HCl	NMe <sub>2</sub> ·HCl	NMe <sub>2</sub> ·HCl	NMe <sub>2</sub> ·H <sub>2</sub> SO <sub>4</sub>	NMe <sub>2</sub> ·H <sub>2</sub> SO <sub>4</sub>	NMe <sub>2</sub> ·HCl	NMe <sub>2</sub> ·HCl	NMe <sub>2</sub> ·HCl	NMe <sub>2</sub> ·HCl	NMe <sub>2</sub> ·HCl	NMe <sub>2</sub> ·HCl
CON(Me) <sub>2</sub>	CON(Me) <sub>2</sub> <sup>d</sup>	CON(Me) <sub>2</sub>	COOH <sup>u</sup>	COOH <sup>u</sup>	COOMe	COOMe	COOMe	COOMe	CO(Et) <sup>v</sup>	CO(Et)
y	x	x	y	x	y	y	x	x	x	x
85-110	127-129	256-258	181-184	110 dec	91-93	224-225	111-113	191-193	110-112	238-239.5
H <sub>2</sub> O	i-PrOAc	EtOH-Et <sub>2</sub> O	H <sub>2</sub> O	EtOH	Hexane	MeOH	Hexane	EtOAc	Hexane	EtOH
C <sub>21</sub> H <sub>27</sub> ClN <sub>2</sub> O·2H <sub>2</sub> O	C <sub>21</sub> H <sub>26</sub> N <sub>2</sub> O	C <sub>21</sub> H <sub>27</sub> ClN <sub>2</sub> O	C <sub>10</sub> H <sub>23</sub> NO <sub>6</sub> S·H <sub>2</sub> O	C <sub>10</sub> H <sub>23</sub> NO <sub>6</sub> S·2H <sub>2</sub> O	C <sub>20</sub> H <sub>23</sub> NO <sub>2</sub>	C <sub>20</sub> H <sub>24</sub> ClNO <sub>2</sub>	C <sub>20</sub> H <sub>23</sub> NO <sub>2</sub>	C <sub>20</sub> H <sub>24</sub> ClNO <sub>2</sub>	C <sub>21</sub> H <sub>25</sub> NO	C <sub>21</sub> H <sub>26</sub> ClNO
35	86	77	83	89	26					
po	ip	ip	ip	ip	ip	ip	ip	ip	ip	ip
3	10	3	3	3	3	3	3	3	3	3
100	300	100	300	100	300	100	100	100	100	>100

<sup>a</sup>x denotes isomer with C<sub>6</sub>H<sub>5</sub> trans to R; y, isomer with these groups cis. <sup>b</sup>Route of administration; doses given in mg/kg calculated as free base. <sup>c</sup>Minimum dose at which behavioral stimulation was observed. <sup>d</sup>Minimum dose at which behavioral depression was observed. <sup>e</sup>Dose causing deaths. <sup>f</sup>Combined yield of 13 and 14. <sup>g</sup>Prepared from the amine and EtOCCl in pyridine at 5°. <sup>h</sup>Prepared from 20 with Br<sub>2</sub> and NaOMe in MeOH. <sup>i</sup>Prepared by LiAlH<sub>4</sub> reduction of the corresponding carbamate. <sup>j</sup>From HCHO·HCOOH and the corresponding primary amine. <sup>k</sup>Configuration unknown. <sup>l</sup>Prepared from 2a by the procedure in ref 5. <sup>m</sup>By hydrogenation of 2a with Raney Ni in (CH<sub>3</sub>CO)<sub>2</sub>O at 50°. <sup>n</sup>Amount isolated pure. <sup>o</sup>Acetylation of 27. <sup>p</sup>From the corresponding nitrile and concentrated H<sub>2</sub>SO<sub>4</sub>, 1 hr at 60°. <sup>q</sup>All efforts to prepare the x isomer from 30 gave 1,4-ethano-2-methyl-1,2,3,4-tetrahydro-3-quinolone [G. Walker and D. Alkalay, *J. Org. Chem.*, **32**, 2213 (1967)]. <sup>r</sup>From the corresponding nitrile and 90% H<sub>2</sub>SO<sub>4</sub>, 4 hr at 96°. <sup>s</sup>From the amine and acid chloride in ether. <sup>t</sup>From the corresponding nitrile refluxed 6 hr in aqueous H<sub>2</sub>SO<sub>4</sub>, bp 145-150°. <sup>u</sup>From 34 and EtMgBr, procedure in the office of the Publication Board, Department of Commerce Report PB 981, p 96A. <sup>v</sup>C: called, 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<sub>2</sub>SO<sub>4</sub> gave with SOCl<sub>2</sub> 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<sup>§</sup> 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<sub>2</sub>NH, giving 11 and 12, respectively. The sulfone 12 was identical with a sample of this compound prepared by another procedure.<sup>9</sup>

The desired acid chlorides 5c subsequently were made from purified 5a sulfates with excess SOCl<sub>2</sub> 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<sub>4</sub> 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 monodecylation of the corresponding 1,4-dinitriles<sup>10,11</sup> 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-

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

mine and sodium methylate in methanol the methyl homolog 21 of compound 17. The  $\text{LiAlH}_4$  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.<sup>12</sup>

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.<sup>13</sup> 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  $\pm 0.4\%$  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  $\text{H}_2\text{O}$  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  $\text{H}_2\text{O}$ . 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  $\text{H}_2\text{O}$ , and dissolved in 1.5 l. of warm PhH. This solution was washed with  $2 \times 200$  ml of  $\text{H}_2\text{O}$ , 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  $\text{NH}_3$  saturated EtOH with Raney nickel and  $\text{H}_2$  at 60 kg/cm<sup>2</sup>, 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 re-

crystallizations 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  $\text{NaBH}_4$  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  $\text{C}_6\text{H}_6$  and  $\text{H}_2\text{O}$ . The solution was concentrated and the carbonyl-free oil in 100 ml of PhH was added to 150 ml of  $\text{SOCl}_2$  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  $\text{Me}_2\text{NH}$  and the mixture was sealed in a pressure bottle and kept at 25° for 4 days. The excess  $\text{Me}_2\text{NH}$  was distilled and the PhMe was washed with  $\text{H}_2\text{O}$  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  $\text{Me}_2\text{NH}$  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  $\text{MeNH}_2$  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  $\text{NaBH}_4$  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  $\text{CHCl}_3$  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  $\text{SOCl}_2$  containing 1.5 ml of  $\text{H}_2\text{SO}_4$ . There was a vigorous evolution of gases. After stirring for 3 days the  $\text{SOCl}_2$  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.* ( $\text{C}_{18}\text{H}_{19}\text{NO}_3\text{S}$ ) 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  $\text{Et}_2\text{O}$  and cold 10%  $\text{Na}_2\text{CO}_3$ . The extract was dried briefly ( $\text{K}_2\text{CO}_3$ ), filtered, and treated with dry HCl. The crystals were filtered and recrystallized from EtOH: yield, 2.9 g; shrinking 200°; mp 233-235°. *Anal.* ( $\text{C}_{18}\text{H}_{17}\text{NO}_2\text{S} \cdot \text{HCl} \cdot \text{H}_2\text{O}$ ) 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  $\text{Me}_2\text{NH}$  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.* ( $\text{C}_{16}\text{H}_{11}\text{O}_3\text{SNa}$ ) C, H.

**Benzo[d]naphtho[2,1-b]thiophene 7,7-Dioxide** (12). The free base from 10 in  $\text{Et}_2\text{O}$  solution rapidly decomposed to 12: mp 235-236°; identical with authentic 12<sup>9</sup> and with material prepared from 11 and poly- $\text{H}_3\text{PO}_4$  by a published procedure.<sup>14</sup>

**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.* ( $\text{C}_{18}\text{H}_{19}\text{ClN}_2$ ) C, H, N.

The free base from this salt and aqueous  $\text{Na}_2\text{CO}_3$  was crystallized from MeCN: mp 190-192°. *Anal.* ( $\text{C}_{18}\text{H}_{18}\text{N}_2$ ) 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  $\text{SOCl}_2$  at 0° and stirred at this temperature until it dissolved, ca. 2 hr. The excess  $\text{SOCl}_2$  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,<sup>10</sup> 103.3 g (0.4 mol), mp 90-110°, and the  $\text{NaNH}_2$  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<sub>2</sub>O and refluxed with 200 ml of H<sub>2</sub>O 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<sub>17</sub>H<sub>17</sub>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

Franco Micheletti Moracci, Felice Liberatore,

*Institute of Applied Pharmaceutical Chemistry, University of Rome, Italy*

Paolo Marchini,\* Gaetano Liso,

*Institute of Organic Chemistry, University of Bari, Italy*

and Mario Cardellini

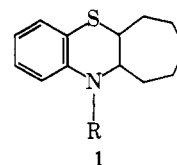
*Institute of Pharmaceutical and Organic Chemistry, University of Camerino, Italy. Received May 29, 1973*

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<sup>1–4</sup>) to be found in the literature, only limited pharmacological data have been described.<sup>2</sup>

**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<sub>4</sub> reduction of the 5a,6,7,8,9,10-hexahydrobenzo[b]cyclohepta[e][1,4]thiazine obtained as previously reported.<sup>5,6</sup>



**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.<sup>7–9</sup>

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)<sup>5,6</sup> 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<sub>2</sub>O, the organic layer was separated, and the aqueous portion was extracted with Et<sub>2</sub>O. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated, and the residue was distilled under vacuum.

Compounds 1a–g were dissolved in anhydrous Et<sub>2</sub>O and the solution was treated with dry HCl until complete precipitation of

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