5-Imino-2-(*p*-aminophenyl)-Δ^2-1,3,4-oxadiazoline Dihydrochloride (3). Method J.—To 10 g (0.05 mole) of **19** in 250 ml of glacial acetic acid heated initially to the boiling point and with the source of heat removed, was added portionwise a total of 10 g of Fe powder; the mixture was stirred an additional 0.5 hr, heated under reflux for 2 hr, and filtered hot. The filtrate was concentrated to dryness *in vacuo*, the residue was shaken with 250 ml of 10% aqueous NH_3, filtered, dried, and extracted with 500 ml of boiling 1-butanol. The butanol extract was concentrated to dryness *in vacuo* and the residue was dissolved in 10% aqueous HCl. The HCl solution was concentrated to dryness *in vacuo* to give **3**. An attempt at catalytic reduction of **19** with Pd–C in glacial acetic acid under 3.5 kg/cm^2 of hydrogen was unsuccessful.

5-Imino-2-(1-ethylpropyl)-Δ^2-1,3,4-oxadiazoline Hydrochloride (12). Method K.—Compound **11** (9.0 g, 0.058 mole) was dissolved in 1:10 absolute ethanol–ether, and the solution was treated with ethereal HCl until acidic to congo red. The precipitate was filtered and air dried to give 9.0 g of **12**.

5-Imino-2-(α-ethylbenzyl)-Δ^2-1,3,4-oxadiazoline Hydrochloride (10). Method L.—To 4.0 g (0.02 mole) of **9** in anhydrous acetone was added 0.02 mole of HCl in absolute ethanol; anhydrous ether was added to turbidity and the whole was cooled to give **10**.

1-Ethyl-3-(5-phenyl-1,3,4-oxadiazol-2-yl)urea (32). Method M.—A solution of 4.5 g (0.028 mole) of **20** in 50 ml of ethyl isocyanate was heated under reflux for 4 hr and then partially concentrated *in vacuo* to give **32**.

5-Imino-2-phenyl-Δ^2-1,3,4-oxadiazoline Maleate (25). Method N.—A mixture of 1.61 g (0.01 mole) of **20**, 1.16 g (0.01 mole) of maleic acid, and 100 ml of propanol was heated to boiling and then cooled to give 2.4 g of **25**.

5-Imino-2-phenyl-Δ^2-1,3,4-oxadiazoline Citrate (26). Method O.—Method N was followed except that 100 ml of acetonitrile was the solvent.

Acknowledgment.—The authors are indebted to Dr. J. Bernstein for discussions helpful in resolving several of the problems during this investigation and to Miss B. Keeler for her assistance in the determination and interpretation of the infrared spectra. Dr. A. Cohen determined the nmr spectra. Several of the compounds were synthesized by Mr. E. J. Pribyl and Mr. C. F. Turk.

Compounds Acting on the Central Nervous System. IV. 4-Substituted 2,3-Polymethylenequinolines

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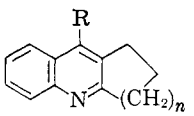
A number of 4-N-substituted amino- and carbamoyl-2,3-polymethylenequinolines have been synthesized and have been found to exhibit a wide spectrum of pharmacological properties, which include analgetic, local anesthetic, analeptic, and respiratory stimulant activities. In particular 4-(4-morpholinyl)-2,3-pentamethylenequinoline has shown significant and promising analeptic and respiratory stimulant activity.

5-Amino-1,2,3,4-tetrahydroacridine (4-amino-2,3-tetramethylenequinoline), although originally synthesized for antibacterial studies,[1] has been shown to possess a wide spectrum of pharmacologial actions, which include anticholinesterase,[2] antagonism to psychotomimetics,[3] morphine antagonist,[4] analeptic,[4c] and decurarizing[5] actions. This molecule seems to offer a good lead for further exploration. Except for an old report of analeptic action of 3,4-dihydro-1,2-benzacridine-5-carboxylic acid[6] (Tetrophan), local anesthetic activity for N,N-diethyl-1,2,3,4-tetrahydroacridine-5-carboxamide[7] and a report published during the course of this work on the analeptic activity of aminocycloheptaquinoline,[8] not much is known about the pharmacology of these compounds. Brian and Souther[9] have recently reported the synthesis of a few more substituted 5-amino-1,2,3,4-tetrahydroacridines but gave no data about their biological activity. The synthesis of a number of 4-N-substituted amino-2,3-polymethylenequinolines (I) and 4-N-substituted carbamoyl-2,3-polymethylenequinolines (II) has now been carried out and their pharmacological actions studied.



I, R=–N< n=1–3
II, R=–CON<

The 4-chloro-2,3-polymethylenequinolines were prepared from the corresponding hydroxy compounds by treatment with phosphorus oxychloride,[10] which on condensation with the appropriate amines in phenol at

(1) A. Albert and W. Gledhill, *J. Soc. Chem. Ind.* (London), **64**, 169 (1945).

(2) (a) F. H. Shaw and G. A. Bentley, *Australian J. Exptl. Biol. Med. Sci.*, **31**, 573 (1953); (b) I. S. De La Lande and G. A. Bentley, *ibid.*, **33**, 555 (1955); (c) E. Heilbronn, *Acta Chem. Scand.*, **15**, 1386 (1961).

(3) S. Gershon, *Nature*, **186**, 1072 (1960).

(4) (a) F. H. Shaw and G. A. Bentley, *Med. J. Australia*, **2**, 868 (1949); (b) *Nature*, **169**, 712 (1952); (c) F. H. Shaw and G. A. Bentley, *Australian J. Exptl. Biol. Med. Sci.*, **33**, 143 (1955); (d) F. H. Shaw, S. Gershon, and G. A. Bentley, *J. Pharm. Pharmacol.*, **9**, 666 (1957).

(5) S. Gershon and F. H. Shaw, *ibid.*, **10**, 638 (1958).

(6) (a) E. Hesse, *Arch. Exptl. Pathol. Pharmakol. Naunyn–Schmiedeberg's*, **111**, 68 (1926); (b) J. Pohl and E. Hesse, *Klin. Wochschr.*, **4**, 344 (1926); *Chem. Abstr.*, **20**, 2204 (1926).

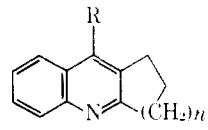
(7) O. Yu Magidson and A. I. Travin, *J. Gen. Chem. USSR*, **7**, 842 (1937).

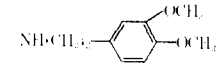
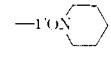
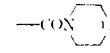
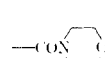
(8) N. Plotnikoff, J. Keith, M. Heimann, W. Keith, and C. Perry, *Arch. Intern. Pharmacodyn.*, **146**, 406 (1963).

(9) W. P. Brian and B. L. Souther, *J. Med. Chem.*, **8**, 143 (1965).

(10) (a) B. K. Blount and S. G. P. Plant, *J. Chem. Soc.*, 376 (1937); (b) L. J. Sargent and L. Small, *J. Org. Chem.*, **11**, 359 (1946).

TABLE I



No.	R	n	% yield	Mp, °C	Formula	% nitrogen Calcd	% nitrogen Found
1	NHC_6H_5	1	38	114	$C_{16}H_{20}N_2$	11.67	11.64
2		1	56	101	$C_{17}H_{20}N_2$	11.10	11.09
3		1	60	144	$C_{16}H_{18}N_2O$	11.02	11.08
4	NHC_7H_7	2	54	65[a]	$C_{67}H_{22}N_2$	...	...
5		2	83	Oil	$C_{28}H_{26}N_2O_2$	7.73	7.78
6		2	64	84	$C_{17}H_{20}N_2$	11.1	11.4
7		2	64	113[b]	$C_{18}H_{22}N_2$	10.53	10.64
8		2	70	143[c]	$C_{17}H_{20}N_2O$	10.45	10.86
9		2	72	94	$C_{18}H_{23}N_3$	14.9	14.5
10		2	51	157–58	$C_{23}H_{25}N_3$	12.2	12.0
11	$CONHC_6H_5$	2	52	127–28	$C_{18}H_{22}N_2O$	9.93	10.01
12	$CON(CH_3)_2$	2	68	128–29	$C_{16}H_{18}N_2O$	11.02	11.12
13	$CON(C_2H_5)_2$	2	56	103[d]	$C_{18}H_{22}N_2O$	...	...
14		2	50	192	$C_{19}H_{22}N_2O$	9.52	9.18
15		2	94	193	$C_{18}H_{20}N_2O_2$	9.46	9.10
16	OC_6H_5	3		128–29	$C_{20}H_{19}NO$	4.84	5.1
17		3	45	110	$C_{18}H_{22}N_2$	10.49	10.01
18		3	30	116–17	$C_{19}H_{24}N_2$	10.00	9.57
19		3	63	123–24	$C_{18}H_{22}N_2O$	9.93	9.60
20		3	54	100	$C_{19}H_{25}N_3$	14.24	13.84
21		3	72	166 dec	$C_{24}H_{33}N_3O_9$[e]	8.28	8.56
22	COOH	3	97	298[f]	$C_{15}H_{15}NO_2$	5.81	5.57
23	$CON(C_2H_5)_2$	3	71	97	$C_{19}H_{24}N_2O$	9.49	9.12
24		3	48	152	$C_{19}H_{22}N_2O_2$	9.03	9.28
25	Cl	3	88	92	$C_{15}H_{14}ClN$	6.05	6.48

[a] Lit.[9] 63–65°. [b] J. V. Braun, A. Heymons, and G. Manz [*Ber.*, **64B**, 227 (1931)] report mp 112°. [c] Lit.[10b] 145–146.5°. [d] Lit.[5] 102–103°. [e] Dioxalate monohydrate. [f] Lit.[11] 292–293°.

temperatures ranging from 120–145° gave the required 4-substituted amino-2,3-polymethylenequinolines, which are described in Table I. The yields obtained in this condensation are very largely dependent on the temperature of the condensation, particularly with the pentamethylene compounds.

For the preparation of compounds of type II, the 4-carboxylic acids were prepared by the condensation of isatin with the appropriate cycloalkanones[11] and converted into the corresponding chloride hydro-

(11) W. Borsche, *Ber.*, **41**, 2203 (1908).

chlorides, which on treatment with the required amines gave various 4-N-substituted carbamoyl-2,3-polymethylenequinolines (Table I).

Experimental Section

4-Chloro-2,3-pentamethylenequinoline (25).—Powdered and dried 4-hydroxy-2,3-pentamethylenequinoline (12.5 g, 0.058 mole) was added under stirring to $POCl_3$ (20 ml, 0.218 mole) over a period of 1 hr. The straw-colored mixture was refluxed for 0.5 hr at 125–130°, poured over 250 g of crushed ice, and stirred vigorously for 1 hr until a clear solution was obtained (warming if necessary). The solution was filtered, cooled, and basified with ammonia, and the product was filtered; yield 12 g (88%). Crystallization from acetone gave an 85% recovery of pure 4-chloro-2,3-pentamethylenequinoline.

4-(4-Morpholinyl)-2,3-pentamethylenequinoline (19).—A mixture of 4-chloro-2,3-pentamethylenequinoline (4.6 g, 0.02 mole) and phenol (3.6 ml, 0.04 mole) was heated at about 100° for 15 min, until a clear solution was obtained. Morpholine (3.6 ml, 0.04 mole) was then added dropwise with stirring and the mixture was heated in an oil bath at 140–145° for 20 hr. The resultant gelatinous mass was poured into 100 ml of water and triturated until it solidified. Water was decanted, the product was taken up in ether and extracted successively with 20% NaOH and water, and the ether layer was dried (Na_2SO_4) and evaporated to dryness. The product was contaminated with 4-phenoxy-2,3-pentamethylenequinoline (**16**). The crude product was taken up in 6 *N* HCl and the less soluble hydrochloride of **16** was filtered, the deep yellow filtrate was extracted exhaustively with ethyl acetate to remove the last traces of impurities, and **19** precipitated from the acid solution with 10% NaOH solution. Crystallization from benzene–hexane (60–70°) gave 3.5 g (63%) of **19** as pale yellow crystals, mp 123–124°.

Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.66; H, 7.85. Found: C, 76.86; H, 7.57.

4-Phenoxy-2,3-pentamethylenequinoline (16) was obtained by warming its hydrochloride with 10% NaOH. Crystallization from cyclohexane yielded boat-shaped platelets, mp 128–129°, infrared 8.25 μ (ArOAr).

Anal. Calcd for $C_{20}H_{19}NO$: C, 83.04; H, 6.92. Found: C, 82.72; H, 7.46.

All of the other substituted **amino-2,3-pentamethylenequinolines** (n = 3) listed in Table I were prepared as above. In the preparation of the **amino-2,3-trimethylenequinolines** (n = 1) the temperature during condensation in phenol was maintained at 135° and the product was worked up as above. A temperature of 120° sufficed for the preparation of **amino-2,3-tetramethylenequinolines** (n = 2) and in this case the crude product was free from 5-phenoxy-2,3-tetramethylenequinoline and only required to be filtered through a short activated alumina column before crystallization.

2,3-Pentamethylenequinoline-4-carboxylic Acid (22).—Isatin (10 g, 0.068 mole) dissolved in 30% aqueous KOH (40 ml, 0.375 mole) was added to an excess of cycloheptanone (20 g, 0.178 mole) dissolved in ethanol (75 ml) and the mixture was kept under reflux for 10 hr. Ethanol was removed under vacuum and the residual syrupy yellow mass was taken up in water (100 ml), the excess cycloheptanone was extracted with ether, the aqueous extract was filtered, and the filtrate was acidified with acetic acid when 2,3-pentamethylenequinoline-4-carboxylic acid slowly crystallized in quantitative yield (16 g). The product was collected and washed with a little ethanol and then water until washings were neutral. It could be crystallized from 100 parts of ethanol.

4-(1-Piperidyl)carbonyl-2,3-tetramethylenequinoline (14).—2,3-Tetramethylenequinoline-4-carboxylic acid hydrochloride (14.1 g, 0.05 mole), prepared by passing a stream of dry HCl through a suspension of the carboxylic acid in dry ether, was dried and mixed intimately with PCl_5 (10.4 g, 0.05 mole). The mixture was shaken on a water bath until the reaction commenced (15 min) and the mixture became a semisolid. Dry thiophene-free benzene (50 ml) was added and the mixture refluxed on the steam bath until no further HCl was evolved (1.5 hr). It was cooled and the product was filtered and washed with more benzene to give 12–14 g of colorless crystals of 2,3-tetramethylenequinoline-4-carbonyl chloride hydrochloride, mp 201–202° dec (lit.[7] 198–200°). The product was dried *in vacuo* over NaOH and used directly for condensation.

A solution of piperidine (2.7 g, 0.03 mole) in dry benzene (10 ml) was added to the above chloride hydrochloride (2.8 g, 0.01 mole) suspended in benzene (5 ml) or dissolved in chloroform (5 ml) and the mixture refluxed for 0.5 hr. The resultant solution was cooled, the piperidine hydrochloride was filtered, and the benzene solution was passed through a short column (10 g) of activated alumina to remove colored impurities. Evaporation and crystallization from benzene–ether gave 1.6 g of **14**, pale yellow plates, mp 192°.

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.55; H, 7.82. Found: C, 77.67; H, 8.07.

All the other **4-N-substituted carbamoyl-2,3-polymethylenequinolines** (n = 2 and 3) listed in Table I were prepared as above.

Pharmacological Activity. Methods.—Acute toxicity and gross observational effects were studied in mice by intraperitoneal administration of the compounds. The anticonvulsant activity in mice was tested against maximal electroshock seizure (MES). The analgetic activity was evaluated by the rat tail method. The local anesthetic activity was tested by the rabbit cornea method, and this activity of the promising compounds was confirmed by intradermal injection in guinea pigs. The effect on blood pressure and respiration was determined in anesthetized cats by intravenous administration. The analeptic activity was determined in mice against phenobarbital, pentobarbital, thiopental, morphine, and ethanol. The promising compounds were studied in detail for their respiratory stimulant activity in rabbits and cats against morphine- and barbiturate-induced depressed respiration. Anticholinesterase activity was determined in rat brain homogenates using acetylthiocholine as substrate.[12]

Results and Discussions

Pharmacological data of the compounds are described in Table II.

Analeptic Action.—Most of the compounds showed central stimulation as evidenced by hyperreflexia, hyperactivity, Straub's phenomenon, and polypnea, followed by clonic and tonic convulsions. The analeptic activity was most marked in 2,3-pentamethylenequinolines (**18–20**) and was particularly significant in **19**; the activity of the latter was, therefore, studied in detail. In mice at $0.5LD_{50}$ it could reduce the sleeping time of 60 mg/kg of pentobarbital by 85% (Table III), and there was cross protection against barbiturate toxicity at different dose levels (Table IV). At $0.5LD_{50}$ the sleeping time of ethanol hypnosis was reduced by 88%. From ethanol, urethan, and chloral hydrate hypnosis at LD_{50} the arousal was instantaneous, but no protection against the toxicity of the drug was afforded.

Respiratory Stimulant Action.—A number of compounds showed polypnea (**4**, **6–8**, **13–15**, **19**, **23**, **24**). This increase in respiration was again most marked in **19**, which was unaffected by carotid and aortic denervation. This compound had no effect on electrical transmission through the superior cervical ganglion of cats. In rabbits it could prevent the death due to respiratory failure by thiopental, pentobarbital, and phenobarbital, and the latter two barbiturates in turn prevented the death due to the very high doses of the compound (Table V) which was more active than 5-amino-1,2,3,4-tetrahydroacridine (THA) (Table V). Nikethamide and prethcamide at similar doses could not prevent the pentobarbital-induced toxicity, while pentylenetetrazole could check the death, but the increase in respiration was not as marked as with **19**.

This respiratory stimulant action was also evident in anesthetized cats and rabbits, where depressed respiration was produced by loading doses of morphine, pentobarbital, and chloralose.

(12) S. S. Parmar, M. Sutter, and M. Nickerson, *Can. J. Biochem. Physiol.*, **39**, 1335 (1961).

TABLE II
PHARMACOLOGICAL ACTIVITY OF SOME OF THE 2,3-POLYMETHYLENEQUINOLINES

No.	Approx LD_{50} (mice), mg/kg ip	Gross observations (mice)	Effect on pentobarbital (60 mg/kg ip) hypnosis (mice) Dose, mg/kg	Effect on pentobarbital (60 mg/kg ip) hypnosis (mice) %	Analgesic activity (rats) Dose, mg/kg ip	Analgesic activity (rats) Intensity, %[b]	Analgesic activity (rats) Duration, min	Local anesthetic activity of a 2% solution (rabbit) Intensity	Local anesthetic activity of a 2% solution (rabbit) Duration, min	Remarks
3	45	Straub tail, hyperreflexia, hypersensitive to touch, persistent clonic convulsions, salivation, and lachrymation.	45	0	4.5	0[c]	...	0	...	Transitory rise in blood pressure.
4	50	Polypnea, persistent clonic convulsions, hyperreflexia, salivation, gasping respiration.	50	0	5	50	30	Complete[d]	>180	*f*
5	100	Hyperreflexia, gasping respiration, cyanosis.	50	0	10	0	...	Complete	>180	*g*
6	75	Polypnea, clonic convulsions, and gasping respiration.	75	0	...	...	...	Complete[d]	>30	...
7	50	Polypnea, preconvulsions, piloerection, salivation, lachrymation, mydriasis, gasping respiration, and death.	50	+50	5	50	45	Complete[d]	>300	Transitory rise in blood pressure.
8	100	Polypnea, clonic convulsion, salivation, lachrymation, mydriasis, locomotor activity reduced.	100	0	10	80	60	0	...	*h*
9	150	Quick and irregular respiration, tail lashing, clonic and tonic convulsions.	120	−35	...	...	...	0	...	...
10	380	At high doses hyperactivity, irritability, straub tail, locomotor activity reduced.	...	...	...	...	...	...	...	Blocked extensor convulsions produced by MES.
13	250	Polypnea, mixed convulsions, hyperreflexia, salivation.	500	0	25	60	20	Partial	15	Transitory rise in blood pressure. Antagonized reserpine-induced crouching.
14	250	Polypnea, persistent clonic convulsion, salivation.	250	0	25	40	15	0[d]	...	...
15	250	Polypnea, clonic and tonic convulsions, hypersensitive to touch, salivation, lachrymation.	500	0	25	60	15	0	...	...
16	1000	Hypersensitive to touch, opisthotonus, clonic and tonic convulsions, lachrymation, salivation.	...	...	100	0	...	...	...	...
17	70	Persistent preconvulsion, clonic and tonic convulsions, hyperreflexia, hyperactive, salivation, lachrymation.	70	+50	7	0	...	Complete	>100	Partially antagonized reserpine-induced ptosis and hypothermia.
18	15	Straub tail, hyperreflexia, hypersensitive to touch, salivation, clonic and tonic convulsions.	15	−80	1.5	0	...	Partial[d]	40	...

TABLE II (*Continued*)

No.	Approx LD_{50} (mice), mg/kg ip	Gross observations (mice)	Effect on pentobarbital (60 mg/kg ip) hypnosis (mice) Dose, mg/kg	Effect on pentobarbital (60 mg/kg ip) hypnosis (mice) Dose, %[a]	Analgesic activity (rats) Dose, mg/kg ip	Analgesic activity (rats) Intensity, %[b]	Analgesic activity (rats) Duration, min	Local anesthetic activity of a 2% solution (rabbit) Intensity	Local anesthetic activity of a 2% solution (rabbit) Duration, min	Remarks
19	50	Polypnea, preconvulsiveness, clonic and tonic convulsions. In rabbits min LD = 5 mg/kg iv; increased rate and depth of respiration, clonic and tonic convulsions.	50	−90	5	70	30	0[d]	...	*i*
20	60	Straub tail, clonic and tonic convulsions, hypothermia.	60	−36	6	0	...	0	...	...
21	110	Straub tail, clonic and tonic convulsions, hypothermia.	110	0	11	50	20	Complete[d]	25	...
23	250	Polypnea, staggering gait, clonic convulvulsions, salivation, hyperreflexia, hyperactive, gasping respiration.	250	+>100	25	40	40	0	...	...
24	250	Polypnea, Straub tail, backward extension of the hind limbs, mixed convulsion, catatonia, mydriasis, salivation, and lachrymation.	250	+>100	25	40	20	0	...	...
THA[e]	30	Tail lashing and whipping, followed by depression, piloerection, tremor, salivation, and lachrymation.	30	0	3	60	45	Complete[d]	120	*j*

[a] Per cent decrease (−) or increase (+) in pentobarbital sleeping time with respect to controls. [b] Per cent of animals showing analgesia. [c] 0 = no effect. [d] Confirmed by intradermal injection in guinea pigs. [e] 5-Amino-1,2,3,4-tetrahydroacridine. [f] Transitory rise in blood pressure. Partial antagonism of reserpine-induced ptosis and crouching in mice. [g] At 2.5 mg/kg iv in cats it showed a 90 mm fall in blood pressure lasting for 12 min. [h] At 2.5 mg/kg iv in anesthetized cats it showed significant increase in rate and depth of respiration lasting for 50 min and transitory rise in blood pressure. [i] At 2.5 mg/kg iv in anesthetized cats it showed a marked increase in the rate and depth of respiration lasting for more than 60 min and transitory rise in blood pressure; partial antagonism of reserpine-induced ptosis and crouching; and reserpine potentiated its convulsive action. [j] At 2.5 mg/kg iv in anesthetized cats it showed slight increase only in the rate of respiration; antagonized completely the crouching and partially the ptosis produced by reserpine while reserpine potentiated its convulsive action in mice.

TABLE III

EFFECT OF **19** AGAINST HYPNOSIS PRODUCED BY 60 MG/KG IP OF PENTOBARBITAL IN MICE[a]

Dose of **19** in LD_{50}	% reduction in sleeping time
0.25	36
0.5	85
1	88

[a] Twelve animals were used at each dose level.

TABLE IV

EFFECT OF **19** ON PENTOBARBITAL TOXICITY IN MICE[a]

Dose of **19** in LD_{50}	Dose of pentobarbital, mg/kg ip 115	125	135	145	175	200
Control	33	83	100	...	...	...
1	...	...	...	...	0	66
2	17	...	...	17	50	50
3	...	...	33	0	...	...
4	33	50	33	25	...	...
6	...	...	100	100	100	...

[a] See footnote *a*, Table III; values are given as per cent deaths.

Anticholinesterase Action.—The results are given in Table VI. The anticholinesterase activity of **19** was much less than that of THA, thus showing that the respiratory stimulant and anticholinesterase activities do not run parallel to each other.

Local Anesthetic Activity.—Some of the compounds (**4–7**, **17**, **21**) including THA showed marked local anesthetic activity both by the rabbit cornea method and the guinea pig intradermal injection. This activity was most prominent in 4-piperidyl compounds. Tetrahydroacridine-5-carboxylic acid diethylamide was described by Magidson, *et al.*,[7] as a local anesthetic; the activity of some of the compounds described in this paper is, however, much more powerful than that of this compound.

Analgetic Activity.—Many compounds showed analgetic activity. No particular structure–activity relationship could, however, be discerned for this activity. 4-(1-Piperidyl)-2,3-tetramethylenequinoline (**7**) was particularly active as an analgetic.

TABLE V

ANTAGONISM OF RESPIRATORY DEPRESSION IN RABBITS

Rabbit no.	Depressant (route)	Dose, mg/kg	Rate of respiration after depressant, no./min	Stimulant	Dose, mg/kg iv	Rate of respiration after stimulant, no./min	Comments
1	Pentobarbital (ip)	75	20	**19**	40	44	Survived
2	Pentobarbital (ip)	75	12	**19**	40	60	Survived
3	Pentobarbital (ip)	75	9	THA	40	22	Death
4	Pentobarbital (ip)	75	Stopped	THA	20	20	Survived
5	Pentobarbital (ip)	75	Stopped	THA	20	0	Death
6	Pentobarbital (ip)	75	20	Pentylenetetrazole	90	35	Survived
7	Pentobarbital (ip)	75	10	Pentylenetetrazole	150	20	Survived
8	Pentobarbital (ip)	75	15	Prethcamide	65	15	Death
9	Pentobarbital (ip)	75	20	Prethcamide	60	16	Death
10	Pentobarbital (ip)	75	20	Prethcamide	120	8	Death
11	Pentobarbital (ip)	75	20	Niketharnide	100	10	Death
12	Pentobarbital (ip)	75	14	Niketharnide	130	14	Death
13	Pentobarbital (ip)	75	10	Niketharnide	500	20	Death
14	Pentobarbital (ip)	75	20	...	...	...	Death
15	Thiopental (iv)	30	Stopped	**19**	5	80	Survived
16	Thiopental (iv)	50	Stopped	**19**	5	50	Survived
17	Thiopental (iv)	50	Stopped	**19**	5	66	Survived
18	Thiopental (iv)	35	Stopped	THA	4	0	Death
19	Thiopental (iv)	25	Stopped	Pentylenetetrazole	40	0	Death
20	Thiopental (iv)	50	Stopped	Pentylenetetrazole	90	0	Death
21	Thiopental (iv)	50	Stopped	Pentylenetetrazole	60	0	Death
22	Thiopental (iv)	25	Stopped	...	...	...	Death
23	Phenobarbital (iv)	300	Stopped	**19**	60	85	Survived
24	Phenobarbital (iv)	300	Stopped	**19**	60	50	Survived
25	Phenobarbital (iv)	300	Stopped	THA	20	0	Death
26	Phenobarbital (iv)	300	Stopped	...	...	...	Death
27	Morphine (iv)	10	28	**19**	2.4[a]	60	Survived
28	Morphine (iv)	10	24	**19**	2[b]	80	Survived
29	Morphine (iv)	10	20	**19**	2.6[c]	70	Survived
30	Morphine (iv)	10	20	THA	3.0[c]	40	Survived
31	Morphine (iv)	10	20	THA	3.0[c]	50	Survived
32	Morphine (iv)	10	20	...	...	...	Survived

[a] In four divided doses. [b] In three divided doses. [c] In six divided doses.

TABLE VI

% INHIBITION OF THE PSEUDOCHOLINESTERASE

Compd	Final concn of the compd	
	$3 \times 10^{-4} M$	$3 \times 10^{-5} M$
THA	100	100
7	82	66.6
17	100	90.0
19	72.7	28.0

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