Spiranes. X. Aminospiranes[1,2a]

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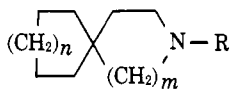
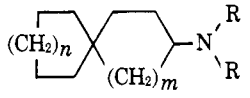
Received June 7, 1965

Aminospiranes have been prepared and examined for pharmacological activity. Those aminospiranes in which the *exo*-nitrogen atom was substituted β or γ to the spiro carbon atom displayed potent analgesic, analeptic, and local anesthetic activity. These activities were either absent or greatly reduced when the *exo*-amino substituent was α to the spiro atom. The aminospiranes were obtained by reduction of the oximes of spiro ketones.

As part of a continuing study of the pharmacological activity of spirane compounds, we have studied the synthesis and physiological effects of various azaspirane derivatives (I). These compounds showed a diversity of biological properties including anticancer, hypotensive, local anesthetic, ganglionic blocking, and tranquilizing activity.[3] Because of this wide span of activity it was of interest to extend our work to include spiranes substituted by amino groups (II) for comparison with those in which the amine function was contained as part of the ring structure (I).



I

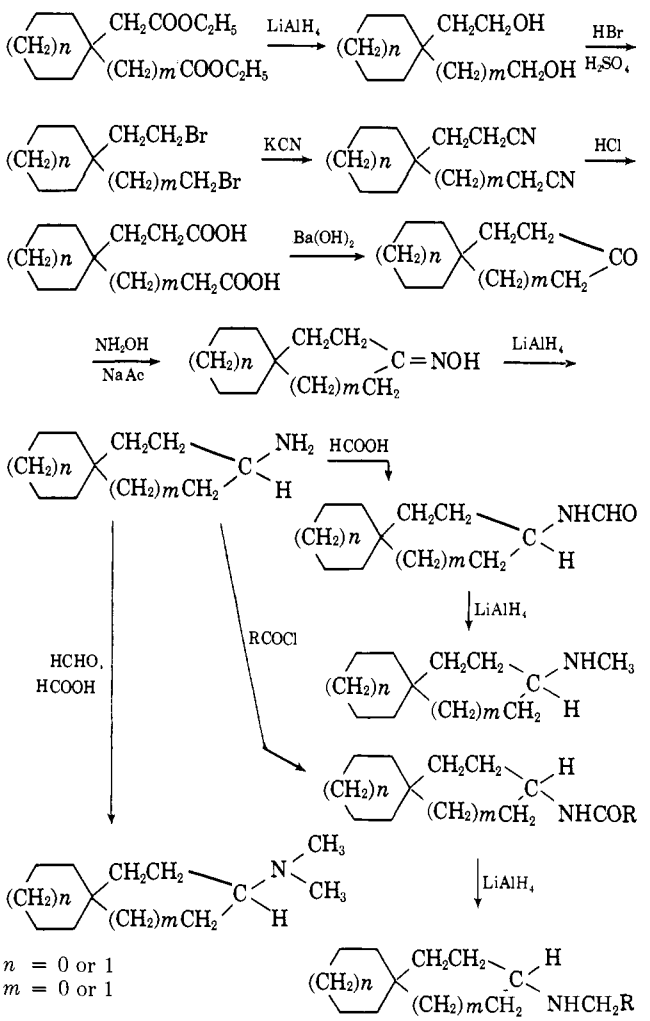


II

$n = 0$ or 1
$m = 1$ or 2

The compounds of the present study were prepared by the reaction sequence shown in Chart I. The cycloalkane-1,1-diacetic acids were obtained by the Guareschi condensation.[4] The cycloalkane-1-carboxy-1-acetic acids were obtained by hydrolysis of the alkali metal cyanide addition product of the cycloalkylidene cyanoacetic esters.[5] The diesters were reduced to the glycols by means of $LiAlH_4$ and converted into the corresponding dibromides with 48% HBr in the presence of sulfuric acid. In all cases the cyclic spiro ether III was formed as a by-product. These ethers could be obtained quantitatively by refluxing the glycol with 48% HBr. The dibromides were converted to the corresponding dinitriles by treatment with KCN in aqueous alcohol. The dinitriles were hydrolyzed to the cycloalkane-1,1-dipropionic acids. This reaction sequence

CHART I



proceeded smoothly in the case of the 1,1-diacetic acids, but conversion of the dibromide from cycloalkane-1-carboxy-1-acetic acids to the corresponding dinitrile gave poorer yields of more difficultly isolable products.

Cyclohexane-1-acetic-1-propionic acid was more readily obtained by the nitric acid oxidation of spiro[5.5]undecan-3-one (IV). This acid had previously been prepared by the oxidation of spiro[5.5]undecan-2-

(1) Part VIII: M. E. Freed and L. M. Rice, in press; part IX: L. M. Rice and C. H. Grogan, in press.

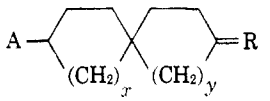
(2) (a) Supported by the D. M. Doyle Pharmaceutical Company, Minneapolis, Minn., and the Tri-Kem Corp., Washington, D. C. (b) Author to whom inquiries should be addressed.

(3) (a) L. M. Rice, C. F. Geschickter, and C. H. Grogan, *J. Med. Chem.*, **6**, 388 (1963); (b) C. H. Grogan, C. F. Geschickter, and L. M. Rice, *ibid.*, **7**, 78 (1964); (c) C. H. Grogan, C. F. Geschickter, and L. M. Rice, *ibid.*, **8**, 62 (1965).

(4) (a) G. A. R. Kon and J. F. Thorpe, *J. Chem. Soc.*, **115**, 701 (1919); (b) I. Guareschi, *Atti. Accad. Sci. Torino*, **36**, 443 (1900/1901).

(5) A. I. Vogel, *J. Chem. Soc.*, 2010 (1928).

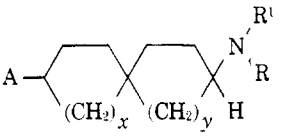
TABLE I
SPIRO KETONES AND OXIMES



No.	R	x	y	A	B.p. (mm.) or m.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	O	1	2	H	100–102 (10)	$C_{10}H_{16}O$	78.90	79.09	10.59	10.86	16.86[a]	16.59
2	O	2	1	H	45–48 (0.3)	$C_{10}H_{16}O$	78.90	79.11	10.59	10.61		
3	O	2	2	CH_3	124–126[b] (10)	$C_{12}H_{20}O$	79.94	79.98	11.18	11.39	15.54[c]	15.72
4	NOH	2	1	H	69–71	$C_{10}H_{17}NO$	71.81	71.88	10.25	9.98	8.38	8.20
5	NOH	2	2	CH_3	115–116	$C_{12}H_{21}NO$	73.80	73.91	10.84	10.95	7.17	7.32
6	NOH	1	2	H	85–87	$C_{10}H_{17}NO$	71.81	71.99	10.25	10.34	8.38	8.42
7	NOH	2	2	H	110–111	$C_{11}H_{19}NO$	72.88	72.97	10.57	10.53	7.73	7.64

[a] 2,4-Dinitrophenylhydrazone, m.p. 163–164°; R. Baird and S. Winstein [*J. Am. Chem. Soc.*, **84**, 794 (1962)] reported m.p. 162–163°. [b] M.p. 60–62°. [c] 2,4-Dinitrophenylhydrazone, m.p. 152–153°.

TABLE II
AMINOSPIRANES



No.	R	R¹	x	y	A	B.p. (mm.) or m.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	2	2	H	110–112[a] (12)	$C_{11}H_{22}ClN$[b,c]	64.84	64.72	10.88	10.94	17.40	17.20	6.87	6.73
2	H	CHO	2	2	H	183–184[a] (5)	$C_{12}H_{21}NO$	73.80	73.63	10.84	10.75			7.17	7.04
3	H	CH_3	2	2	H	112–114[a] (9)	$C_{12}H_{24}ClN$[d,e]	66.49	66.71	10.69	10.90	16.28	16.10	6.46	6.38
4	CH_3	CH_3	2	2	H	122–124[a] (9)	$C_{13}H_{26}ClN$[f,g]	67.35	67.22	11.31	11.39	15.30	15.13	6.04	6.16
5	H	H	1	2	H	88–90[a] (10)	$C_{16}H_{20}ClN$[h]	63.30	63.52	10.62	10.91	18.70	18.75	7.38	7.23
6	H	H	2	2	CH_3	...	$C_{12}H_{24}ClN$[i]	66.49	66.80	10.69	10.96	16.28	16.32	6.46	6.41
7	H	H	2	1	H	83–85[a] (5)	$C_{16}H_{29}ClN$[j,k]	63.30	63.46	10.62	10.87	18.70	18.61	7.38	7.35
8	H	C_3H_7CO[l]	2	2	H	78–80	$C_{15}H_{27}NO$[m]	75.89	75.97	11.47	11.63			5.90	5.85
9	H	C_4H_9[n]	2	2	H	283–284	$C_{17}H_{30}ClN$[o]	69.32	69.08	11.64	11.48	13.64	13.54	5.39	5.50
10	H	C_6H_5CO[p]	2	2	H	139–140	$C_{18}H_{25}NO$[m]	79.65	79.63	9.29	9.38			5.16	5.02
11	H	$C_6H_5CH_2$[q]	2	2	H	241–242	$C_{18}H_{28}ClN$[o]	73.56	73.35	9.60	9.80	12.07	11.98	4.77	4.92
12	H	C_6H_4ClCO[r]	2	2	H	140–141	$C_{18}H_{24}ClNO$[m]	70.68	70.38	7.91	7.88	11.59	11.40	4.58	4.51
13	H	$C_6H_4ClCH_2$[s]	2	2	H	243–244	$C_{18}H_{27}ClN$[o]	65.84	65.77	8.28	8.20	21.60	21.56	4.27	4.24
14	H	$CH_3C_6H_4CO$[t]	2	2	H	139–140	$C_{19}H_{27}NO$[m]	79.95	79.98	9.54	9.40			4.91	4.88
15	H	$CH_3C_6H_4CH_2$[u]	2	2	H	262–263	$C_{19}H_{30}ClN$[o]	74.11	74.02	9.82	9.90	11.52	11.36	4.55	4.42

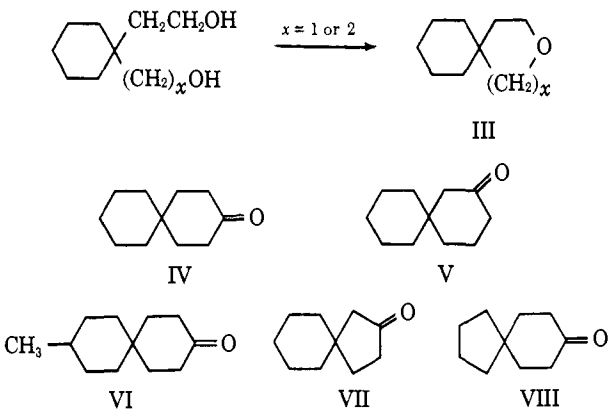
[a] Base. [b] Hydrochloride, m.p. 298–300°. [c] Picrate, m.p. 231–232°. *Anal.* Calcd. for $C_{17}H_{24}N_4O_7$: N, 14.15. Found: N, 14.26. [d] Hydrochloride, m.p. 171–172°. [e] Picrate, m.p. 151–153°. *Anal.* Calcd. for $C_{18}H_{26}N_4O_7$: N, 13.65. Found: N, 13.35. [f] Hydrochloride, m.p. 283°. [g] Picrate, m.p. 177–178°. *Anal.* Calcd. for $C_{19}H_{28}N_4O_7$: N, 13.20. Found: N, 13.40. [h] Hydrochloride, m.p. 324–326°. [i] Hydrochloride, m.p. 293–296°. [j] Hydrochloride, m.p. 258–260°. [k] Picrate, m.p. 190–191°. *Anal.* Calcd. for $C_{16}H_{22}N_4O_7$: N, 14.65. Found: N, 14.60. [l] Butyryl. [m] Amide. [n] Butyl. [o] Hydrochloride. [p] Benzoyl. [q] Benzyl. [r] *m*-Chlorobenzoyl. [s] *m*-Chlorobenzyl. [t] *p*-Methylbenzoyl. [u] *p*-Methylbenzyl.

one (V).[6] As the ketone IV was more readily prepared than V, the oxidation of IV represents an improvement in the synthesis of cyclohexane-1-acetic-1-propionic acid.

Cyclization of the acids to the desired spiro ketones, obtained in good yields as colorless oils, was effected by pyrolysis in the presence of barium hydroxide. Spiro ketones prepared are shown by IV, VI, VII, and VIII. Conversion to the oximes was nearly quantitative. These are listed in Table I.

Reduction of the 2- or 3-substituted spiro ketoximes to the corresponding aminospiranes proceeded smoothly in excellent yield with $LiAlH_4$. All of the aminospiranes were stable, distillable, colorless oils. These amines, together with derivatives, are shown in Table II. In the case where 1-aminospiranes were required for pharmacological comparison, reduction of the spirane-1-ketoximes with $LiAlH_4$ did not proceed to any appreciable extent. Large amounts of starting ketoxime were recovered unchanged. Successful reduction to the desired 1-aminospiranes was achieved with sodium in alcohol.

(6) W. S. G. P. Norris, *J. Chem. Soc.*, 245 (1926).



The aminospiranes were methylated by means of formic acid and formaldehyde. Monomethylation was accomplished by formylation and reduction. The amines were acylated directly or by the Schotten–Baumann method and the amides thus obtained were reduced to N-substituted aminospiranes.

Pharmacology

The aminospiranes were studied for pharmacodynamic and therapeutic potentialities. The compounds, 3-aminospiro[5.5]-undecane, 1-aminospiro[5.5]undecane, and 2-aminospiro[4.5]-decane, as their hydrochloride salts, were evaluated for analgesic action by the rat-tail squeal test, a modification of the Reinhard and de Beer mouse squeal test.[7] Meperidine hydrochloride was used for comparison. In these studies each group of rats was tested prior to administration of any drug and only those rats which demonstrated a squeal reflex were used. Prior to drug administration a comparative value for the pain threshold for each rat was determined by applying current from a Harvard inductorium to a Harvard platinum electrode applied approximately 2.5 cm. from the base of the tail which had been wet with saline. The current was progressively increased until the rat squealed; the average of two such readings was used as the baseline value. Following administration of drugs the test was repeated at 0.5- and 3-hr. intervals.

The difference between the pre- and postadministration values (identified as Δ in Table III) established the extent to which the pain threshold had been modified. A minus Δ indicates an analgesic effect; the higher the value the greater the analgesia. A positive Δ indicates an increase in sensitivity to pain.

In all of the tests the compounds were administered intramuscularly to 140–160-g. rats. Relative values of current are based on a scale of 0–12. A reading of "12" indicates no current and a reading of "0" maximum current. The data from these tests are summarized in Table III. From the data in Table III it is evident that 3-aminospiro[5.5]undecane is a potent analgesic. It appears to have a faster onset but a shorter duration of action than meperidine in rats.

Analeptic Effects.—3-Aminospiro[5.5]undecane exhibited potent respiratory stimulant and analeptic effects in the rat, rabbit, and Rhesus monkey. In the rabbit (4 kg.) a dosage of 50 mg. of this compound antagonized the effects of 11 mg. of morphine sulfate whether administered before or after the morphine.

In a series of 50 rats the effects of 10 mg. of pentobarbital were antagonized by a dose of 5 or 10 mg. of 3-aminospiro[5.5]undecane hydrochloride. In another series of 20 rats the narcotic effect of 15 mg. of meperidine was antagonized by 10 mg. of this compound. Another series of rats was administered toxic doses (10 mg./150-g. rat) of pentobarbital. 3-Aminospiro[5.5]undecane protected against the toxic effects of this hypnotic.

In a 5.5-kg. Rhesus monkey, which had been repeatedly anesthetized with pentobarbital for surgery, a single preadministered dose of 30 mg. i.m. of 3-aminospiro[5.5]undecane blocked the hypnotic action of 50 mg. of pentobarbital administered intravenously. A second and a third dose of 50 mg. of pentobarbital administered intravenously at 10-min. intervals after the initial dose (total dose of 150 mg. within 0.5 hr.) were without hypnotic effect up to 6 hr. of observation.

It is thus apparent that 3-aminospiro[5.5]undecane is a powerful respiratory stimulant before or after the administration of barbiturates and meperidine. Drug-induced abdominal respiration is elevated to the thoracic region. The toxic and hypnotic effects of intravenously administered pentobarbital were blocked by 3-aminospiro[5.5]undecane.

Local Anesthetic Activity.—In a series of 5 rats (175 g.) 2-aminospiro[4.5]decane hydrochloride (25 mg. in 0.35 ml. of 0.9% saline) injected intramuscularly in the hind leg produced immediate paralysis of the limb which lasted for at least 24 hr. After 72 hr. the effect was gone and the animals were normal.

In another test 5 rats (175 g.) were injected with 1 mg. of this compound in saline in the thigh adjacent to the sciatic nerve. All rats exhibited motor paralysis in the injected leg within 3 min. In 1.5 hr. the motor anesthesia was decreasing and motor function returning. In 2.5 hr. the injected limbs were functionally normal. None of the animals exhibited discomfort when the drug was injected.

When 3-aminospiro[5.5]undecane and 1-aminospiro[5.5]undecane hydrochlorides were similarly assayed, the former showed slight and the latter no anesthesia over a 4-hr. period.

Rabbit Cornea Assay.—A 2% solution of 2-aminospiro[4.5]-decane hydrochloride in distilled water was applied to the rabbit cornea for 1 min. by cupping the lower lid. A glass rod was touched to the cornea and the presence or absence of the wink reflex recorded against time. Four drops of the solution were applied to the right eye and the left eye was used as the control. Application produced blinking, the eye lids closed, and the rabbit tried to move back in the restraining box. After 2 min. the lids opened and the animal relaxed. The wink reflex was tested at 5-min. intervals until it returned to normal. Typical data are shown in Table IV.

TABLE III
ANALGESIC TESTS

Dose, mg.	Before[a]	After 30 min.[a]	Δ	After 3 hr.[b]	Δ
		3-Aminospiro[5.5]undecane[b]			
3	9.5	7.5	−2	10	+0.5
4	7.5	9	+1.5	9	+1.5
5	7.5	5.5	−2	6.5	−1
6	9.5	5	−4	8.5	−1
7	8	5	−3	6	−2
8	8.75	7.5	−1.25	7.5	−1.25
Control	7.5	7.5	0	7	−0.5
		1-Aminospiro[5.5]undecane[b]			
3	4	5	+1	5	+1
4	4	5.5	+1.5	5.5	+1.5
5	5	6	+1	6	+1
6	4	6	+2	6	+2
7	5	5.5	+0.5	5.75	+0.75
8	4	5.5	+1.5	6	+2
Control	5.5	5	−0.5	5.5	0
		2-Aminospiro[4.5]decane[b]			
5	2.5	4.5	+2	4.5	+2
6	2	2	0	5	+3
7	4	5.5	+1.5	7	+3
8	5	5	0	6	+1
9	5	5	0	5	+0
10	3	3	0	6	+3
Control	4	4	0	4.5	+0.5
		Meperidine			
3	7.25	7.25	0	7.75	+0.5
4	8	9.5	+1.5	6	−2
5	7.5	6.25	−1.25	3.5	−4
6	7.75	7.5	−0.25	4.25	−3.5
7	9.5	6.25	−3.25	6	−3.5
Control	7	8	+1	7.25	+0.25

[a] Current reading, scale 0–12. [b] Administered as the hydrochlorides in aqueous solution.

(7) (a) M. F. Lockett and M. M. Davis, *J. Pharm. Pharmacol.*, **10**, 80 (1958); (b) F. E. Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941).

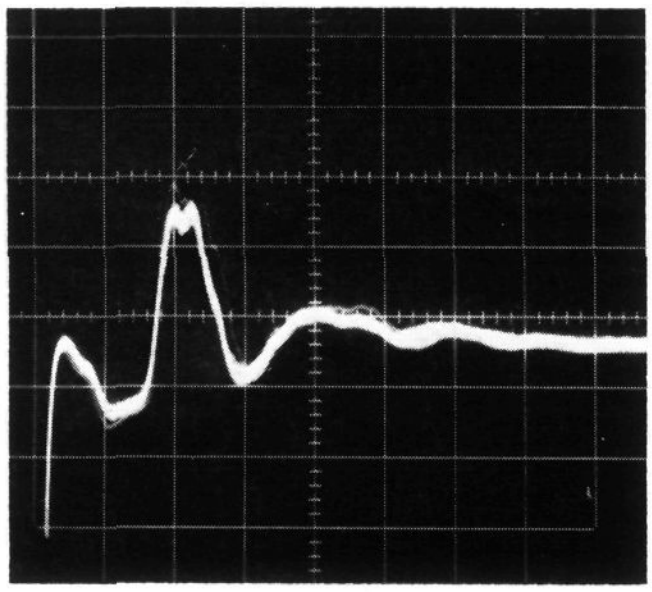


Figure 1.—Normal action potential of a frog nerve.

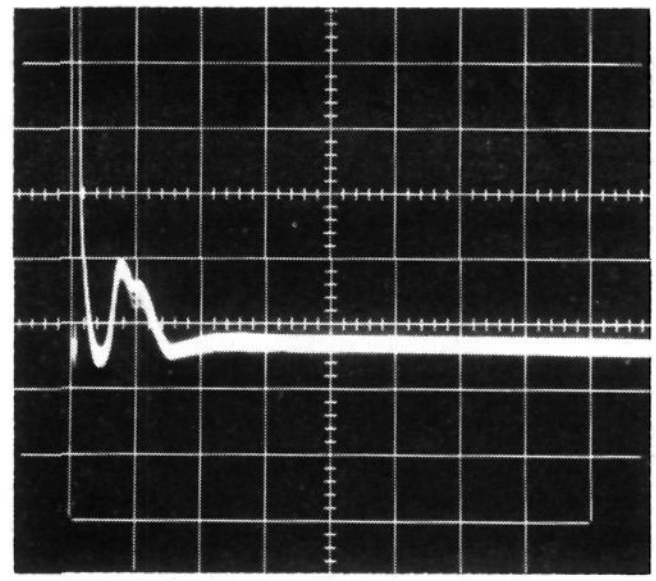


Figure 2.—Action potential of a frog nerve 2 min. after the application of 2-aminospiro[4.5]decane hydrochloride.

TABLE IV

Time, min.	Observation
5	Depressed reflex
10	Depressed reflex
15	No reflex
20	No reflex
25	No reflex
30	Depressed reflex
35	Normal reflex

No appreciable vasodilation (irritation) was evident over a 4-hr. observation period and the eye was normal in appearance 60 hr. later.

Frog Sciatic Nerve Preparation.—Further evidence of the anesthetic and nerve-blocking activity of 2-aminospiro[4.5]-decane hydrochloride was obtained by applying the drug as a 2% solution in distilled water directly to the frog's sciatic nerve and measuring the action potential.

The sciatic nerve was freed of tissue for 2 cm., over which the action potential was recorded. The nerve was stimulated for 500 μsec. at 1.5 v., 30 c.p.s. The action potentials were picked up by gold plated electrodes printed on a plastic circuit board, which was inserted under the nerve *in situ* and fed to a high-sensitivity oscilloscope. The oscilloscope screen was photographed to provide permanent records.

The normal action potential is shown by Figure 1. Figures 2 and 3 show the action potential decrement which began within 2 min. and continued during the experiment, approximately 1 hr. These results are characteristic of local anesthetic drugs when studied under similar conditions.[8]

Experimental Section

All melting points were obtained with a Thomas–Hoover capillary-type apparatus and are corrected. Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

Dibromides and glycols were all obtained by reduction of the corresponding diester and reaction of the diglycol[1] with HBr and H_2SO_4.

1,1-Bis(β-cyanoethyl)cyclopentane.—A solution of 150 g. of 1,1-bis(β-bromoethyl)cyclopentane dissolved in 750 ml. of 80% alcohol was added rapidly with stirring to a solution of 85 g. of KCN in 500 ml. of 80% alcohol. The mixture was refluxed for 8 hr., cooled, and filtered. After pouring into 2 l. of ice water, the product solidified and was filtered, washed with ice water, and dried (82 g., 88%). On distillation the product was obtained: 72 g., b.p. 135–140° (0.1 mm.). It melted at 30–31° on recrystallization from hexane.

Anal. Calcd. for $C_{11}H_{16}N_2$: C, 74.96; H, 9.15; N, 15.89. Found: C, 75.24; H, 9.09; N, 16.01.

1,1-Bis(β-cyanoethyl)-4-methylcyclohexane was prepared in an analogous manner to the above dicyano compound from 42.5 g. of 1,1-bis(β-bromoethyl)-4-methylcyclohexane and 40.5 g. of KCN. The product did not solidify and was extracted with ether and dried. On distillation the oil boiled at 138–142° (0.05 mm.) and weighed 24.5 g.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.32; H, 9.64; N, 13.95.

Cyclopentane-1,1-bispropionic Acid.—To 500 ml. of concentrated HCl was added 72 g. of 1,1-bis(β-cyanoethyl)cyclopentane, and the mixture was refluxed for 24 hr. On cooling, the product crystallized and was filtered and washed with water. The crude acid was dissolved in $KHCO_3$ solution, decolorized with charcoal, and filtered, and the solution was acidified with HCl. After drying, the product (73 g.) melted at 99–100° which did not change on recrystallization from benzene.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.96; H, 8.56.

4-Methylcyclohexane-1,1-bispropionic Acid.—Hydrolysis of the corresponding dinitrile (23 g.) as in the above example yielded the product (24 g.) which on recrystallization from benzene melted at 121–122°.

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.18; H, 9.32.

Cyclohexane-1-acetic-1-propionic Acid.—To 120 ml. of refluxing concentrated HNO_3 was added dropwise 30 g. of spiro[5.5]undecan-3-one and the mixture was refluxed an additional 20 min. After cooling, the mixture was diluted with 3 vol. of water and was allowed to crystallize. The crude product (18 g.), m.p. 130–140°, was dissolved in $KHCO_3$, decolorized, and acidified with HCl. The acid melted at 138–140°, and recrystallization from chloroform–petroleum ether raised the melting point to 141–142°, lit.[6] 142.5°.

Spiro ketones were prepared by the pyrolysis of the dipropionic acids as previously described[9] and are listed in Table I.

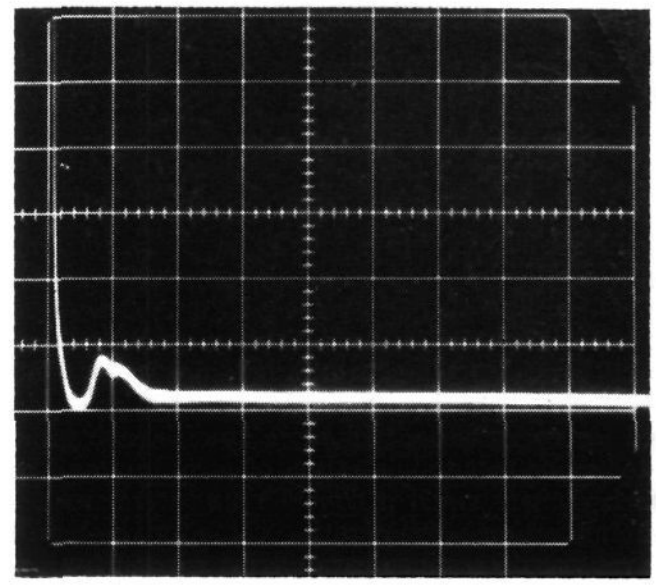


Figure 3.—Action potential of a frog nerve 1 hr. after the application of 2-aminospiro[4.5]decane hydrochloride.

(8) G. A. Condouris and J. W. Kiraly, *J. Am. Dental Surg. Assoc.*, **8**, 3 (1961).

(9) L. M. Rice, M. E. Freed, and C. H. Grogan, *J. Org. Chem.*, **29**, 2637 (1964).

Oximes were prepared as illustrated by the following general example.

Spiro[5.5]undecane-3-ketoxime.—A mixture of 50 g. of hydroxylamine hydrochloride and 60 g. of sodium acetate was dissolved in the least amount of water to give a clear solution at 40°. Spiro[5.5]undecan-3-one (55 g.) was added with stirring and the mixture was vigorously shaken for 1 hr. The precipitated product was filtered, washed with water, and dried. After drying, the product (60 g.) melted at 109–110°. Recrystallization from methanol and water yielded the pure material, m.p. 110–111°.

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.93. Found: C, 72.97; H, 10.53, N, 7.64.

The spiroamines were all prepared by the following general method.

3-Aminospiro[5.5]undecane.—The above oxime (50 g.) was dissolved in anhydrous ether and was slowly added to a solution of 25 g. of $LiAlH_4$ in 1 l. of anhydrous ether. After stirring 3 hr., the mixture was decomposed with water in the usual manner and filtered. The ethereal solution was dried, and the ether was stripped off. Vacuum distillation of the residue gave the product (38 g., 82%), b.p. 110–112° (12 mm.). Conversion in the usual manner with alcoholic HCl and ether gave the hydrochloride, m.p. 298–300°.

Anal. Calcd. for $C_{11}H_{22}ClN$: C, 64.84; H, 10.88; Cl, 17.40; N, 6.87. Found: C, 64.72; H, 10.94; Cl, 17.20; N, 6.73.

The **picrate** was prepared in the usual manner using methanol as a solvent and adding water until precipitation started; m.p. 231–232°.

Anal. Calcd. for $C_{17}H_{24}N_4O_7$: N, 14.13. Found: N, 14.26.

The **phenylthiourea** was prepared in hexane and after recrystallization from methanol melted at 156–157°.

Anal. Calcd. for $C_{18}H_{26}N_2S$: C, 71.47; H, 8.66; N, 9.26. Found: C, 71.74; H, 8.87; N, 9.03.

N-Formyl-3-aminospiro[5.5]undecane.—To a solution of 8.3 g. of 3-aminospiro[5.5]undecane in 25 ml. of alcohol was added 4.7 g. of formic acid. The resultant mixture was heated at reflux and the excess formic acid was stripped off. The residue on distillation yielded 7 g. of product, b.p. 183–184° (5 mm.).

Anal. Calcd. for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.63; H, 10.75; N, 7.04.

N-Methyl-3-aminospiro[5.5]undecane.—Reduction of the above formyl derivative in the usual manner with $LiAlH_4$ gave the product, b.p. 112–114° (9 mm.), which was converted to the hydrochloride, m.p. 172–173°.

Anal. Calcd. for $C_{12}H_{24}ClN$: C, 66.49; H, 10.69; Cl, 16.28; N, 6.46. Found: C, 66.71; H, 10.90; Cl, 16.10; N, 6.38.

N,N-Dimethyl-3-aminospiro[5.5]undecane.—To 8.3 g. of 3-aminospiro[5.5]undecane was added 12.8 g. of formic acid in portions with intermediate cooling. After standing for 10 min., 12 ml. of 37% formaldehyde was added with stirring. The mixture was refluxed for 4 hr., allowed to cool, and stripped. The residue was dissolved in 10% HCl, and the solution was filtered, cooled, neutralized with NaOH, and extracted with ether. After drying (Na_2SO_4) the ether was removed and the residue was distilled, b.p. 122–124° (9 mm.), yield 6.3 g. The oil was converted directly into the **hydrochloride,** m.p. 283°, yield 6.3 g.

Anal. Calcd. for $C_{13}H_{26}ClN$: C, 67.35; H, 11.31; Cl, 15.30; N, 6.04. Found: C, 67.22; H, 11.39; Cl, 15.13; N, 6.16.

N-Benzoyl-3-aminospiro[5.5]undecane.—The usual procedure of the Schotten–Baumann reaction was employed and 8 g. of product was obtained from 5 g. of the amine. Recrystallization from methanol gave the pure material, m.p. 139–140°.

Anal. Calcd. for $C_{18}H_{25}NO$: C, 79.65; H, 9.29; N, 5.16. Found: C, 79.63; H, 9.38; N, 5.02.

N-Benzyl-3-aminospiro[5.5]undecane.—The preceeding amide on reduction with $LiAlH_4$ in the usual manner yielded the product which was converted directly to the **hydrochloride,** m.p. 241–242° (from water).

Anal. Calcd. for $C_{18}H_{28}ClN$: C, 73.56; H, 9.60; Cl, 12.07; N, 4.77. Found: C, 73.35; H, 9.80; Cl, 11.98; N, 4.92.

Structure–Activity Relationships in the Cyproheptadine Series

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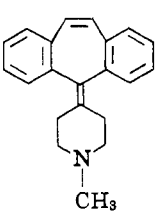
Received June 1, 1965

A series of compounds related to cyproheptadine has been prepared and the antihistaminic and antiserotonin properties were studied. The structural variations include: replacement of the methyl on nitrogen by other groups, introduction of halogen substituents in the aromatic nucleus, saturation of the 5,α or the 10,11 double bond, and replacement of the dibenzocycloheptene nucleus by xanthene, thioxanthene, or fluorene systems. The antihistaminic and antiserotonin actions of the thioxanthene congener closely approximate those of cyproheptadine. All other compounds, with the exception of the N-ethyl analog of cyproheptadine, were less active.

Cyproheptadine (I) was prepared in the course of synthesis of a series of dialkylaminopropylidenedibenzocycloheptenes for study as tranquilizing agents.[1] It proved to be without notable action on the central nervous system; however, the antihistamine and antiserotonin activities that are rather widely distributed throughout the series were found to be exceptionally prominent in this compound.[2] These properties led to the introduction of cyproheptadine as an antipruritic drug.[3]



I

In order to elucidate structure–activity relationships, twenty-one related compounds were synthesized and

(1) E. L. Engelhardt, M. E. Christy, H. C. Zell, C. M. Dylion, M. B. Freedman, and J. M. Sprague, Abstracts of Papers, 141st National Meeting of the American Chemical Society, Washington, D. C., March 1962, p. 4N.

(2) C. A. Stone, H. C. Wenger, C. T. Ludden, J. M. Stavorski, and C. A. Ross, *J. Pharmacol. Exptl. Therap.*, **131**, 73 (1961).

(3) Periactin®.