Spiranes. XII. Azaspiranylalkylphenothiazines[1]

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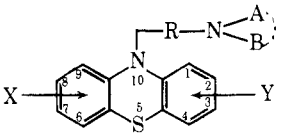
10-Azaspiranylalkylphenothiazines and one 10-isoindolinylalkylphenothiazine have been synthesized and screened for CNS depressant properties. When tested in rats several of these compounds exhibited an order of activity comparable to that of chlorpromazine. An azaspiranyl analog of chlorpromazine was considerably more potent than the latter.

Although phenothiazine has long been used as an effective insecticide and anthelmintic, it was not until the synthesis of promazine[2] and promethazine[3] by Charpentier[4] in 1944 and the elaboration of the potent antihistaminic properties[5] of these 10-dialkylaminoalkylphenothiazines that the phenothiazine nucleus became of importance in medicinal chemistry. Continued investigation of 10-substituted phenothiazines[6] led to the synthesis of chlorpromazine[7] and the discovery of its potent CNS depressant properties.[8]

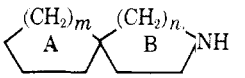
As a result of the investigations of the French workers on the synthesis and application of phenothiazine derivatives in the treatment of mental disorders,[9-11] hundreds of permutations of the basic active structure, I, have evolved in the last two decades. Many of the initial variations were performed by Charpentier.[12]



I

Structural features necessary for optimal CNS effects are, briefly, as follows. Substituent X on positions 6–9 has little effect on activity; R is a three-carbon chain; the tertiary amine moiety $-N\langle^{A}_{B}$ is a small heterocyclic ring or A and B are methyl or ethyl; and Y is an atom or group providing a high electron density, such as halogen, trifluoromethyl, dimethylaminosulfonyl, acyloxy, alkoxy, alkylthio, preferably at the 2 position. When R is ethylene or the tertiary amine moiety is substituted at the 2 position of a trimethylene chain, antihistaminic and spasmolytic properties are more pronounced.

Since we had recently synthesized a new group of secondary amines, the azaspiranes[13] II, it was of interest to investigate the type of activity and potency of the phenothiazine derivatives in which the tertiary amine moiety of I was an azaspiranyl group.



II, $n = 1$ or 2; $m = 1$–4

The only reports of azaspiranylalkylphenothiazines in the literature are those of Moffett, *et al.*,[14] who reported the synthesis of 10-(α,α-polymethylenespiropyrrolidino)alkylphenothiazines in which the pyrrolidine nitrogen atom was α to the spiro carbon. It has been our experience in the pharmacological evaluation of a series of CNS depressants (ω-azaspiranylbutyrophenones[15]) that when the ring nitrogen atom was α to the spiro carbon, activity was greatly decreased or abolished as compared to the potent activity of isomeric derivatives in which the spiro carbon was β or γ to the ring nitrogen. The same type of observations extended to a group of *exo*-nitrogen-substituted spirane nuclei (aminospiranes[15]). When the amino group was β or γ to the spiro carbon atom, potent analgesic, local anesthetic, and respiratory stimulants resulted, while isomeric α-substituted aminospiranes exhibited little or no pharmacological activity in these areas.

Moffett[14] claimed only that the 10-(α,α-polymethylenespiropyrrolidino)alkylphenothiazines increased the sleeping time of mice administered hexobarbital, and no specific CNS pharmacological activity was cited.

(1) Part XI: L. M. Rice, K. R. Scott, and C. H. Grogan, *J. Med. Chem.*, **9**, 765 (1966).

(2) 10-(3-Dimethylaminopropyl)phenothiazine hydrochloride.

(3) 10-(2-Dimethylaminopropyl)phenothiazine hydrochloride.

(4) P. Charpentier, *Compt. Rend.*, **225**, 306 (1947).

(5) (a) B. N. Halpern and R. Ducrot, *Compt. Rend. Soc. Biol.*, **140**, 361 (1946); (b) B. N. Halpern, *ibid.*, **140**, 363 (1946).

(6) P. Charpentier, U. S. Patent 2,519,886 (1950).

(7) (a) P. Charpentier, P. Gailliot, R. Jacob, J. Gaudechon, and P. Buisson, *Compt. Rend.*, **235**, 59 (1952); (b) 2-chloro-10-(3-dimethylaminopropyl)phenothiazine hydrochloride.

(8) J. Delay and P. Deniker, *Thérapie*, **8**, 347 (1953).

(9) W. Wirth, *Med. Chemie, Abhandl. Med. Chem. Forschungsstaetten Farbwerke Hoechst, A. G.*, **7**, 37 (1963).

(10) D. Bovet, *Pure Appl. Chem.*, **6**, 383 (1963).

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(12) P. Charpentier, U. S. Patent 2,645,640 (1953).

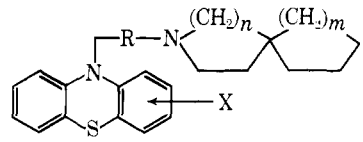
(13) C. H. Grogan, C. F. Geschickter, M. E. Freed, and L. M. Rice, *J. Med. Chem.*, **8**, 62 (1965).

(14) (a) R. B. Moffett, U. S. Patent 2,814,622 (1957); (b) R. B. Moffett and R. D. Aspergren, *J. Am. Chem. Soc.*, **82**, 1600 (1960).

(15) L. M. Rice, E. C. Dobbs, and C. H. Grogan, *J. Med. Chem.*, **8**, 825 (1965).

TABLE I

AZASPIRANYLALKYLPHENOTHIAZINES



No.	R	m	n	X	Yield, %	HCl salt mp, °C	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
1	3-Propyl[a]	2	2	H	78	227–228	$C_{25}H_{33}ClN_2S$	69.98	69.94	7.75	7.84	6.53	6.39
2	3-Propyl	2	2	H	79	217–218	$C_{26}H_{35}ClN_2S$	70.48	70.27	7.96	7.87	6.32	6.50
		9-Methyl											
3	3-Propyl	3	1	H	53	176–177	$C_{25}H_{33}ClN_2S$	69.98	70.15	7.75	7.95	6.53	6.80
4	3-Propyl	1	2	H	72	225–226	$C_{24}H_{31}ClN_2S$	69.45	69.67	7.53	7.66	6.75	6.89
5	2-Propyl	1	2	H	65	232–234 dec	$C_{24}H_{31}ClN_2S$	69.45	69.40	7.53	7.51	6.75	6.84
6	3-Propyl	1	2	H	84	228–228.5	$C_{25}H_{33}ClN_2S$	69.98	70.28	7.75	7.96	6.53	6.40
		3-Methyl											
7	3-Propyl	2	2	2-Cl	52	205–206	$C_{25}H_{32}Cl_2N_2S$	64.78	64.68	6.96	7.21	15.30[b]	15.12[b]
8	3-Propyl	1	1	H	..	62–64[c]	$C_{30}H_{38}N_2O_7S \cdot H_2O$[c]	61.20	60.93	6.85	6.96	4.76	4.53
		7-Methyl											
9	3-Propyl	d	2	H	75	130–134	$C_{29}H_{39}ClN_2S$	72.09	71.83	8.14	8.25	5.80	6.00
10	3-Propyl	e		H	62	128–130	$C_{24}H_{29}ClN_2OS$	67.19	67.16	6.81	7.14	6.53	6.31

[a] Numbers preceding the central chain, R, refer to the position of attachment of the azaspiranyl moiety to R. [b] Chlorine analyses. [c] The hydrochloride of this material was tacky and hygroscopic and would not crystallize. Of the several salts tried, only a crystalline citrate hydrate was finally obtained. The data presented are for the citrate. [d] The azaspiranyl moiety in this case is spiro-*trans*-decalin-2,4′-piperidine. [e] The ring system attached to R in this case is 4-methyl-4,7-epoxyhexahydroisoindoline.

TABLE II

PHARMACOLOGICAL OBSERVATIONS[a]

No.	LD_{50},[b] mg/kg	ED_{50},[c] mg/kg	Effect duration, hr	Dose producing effect for 24 hr or longer, mg/kg
1	175	<10	3–6	~50
2	200	<5	3–5	~50
3	125	5	2–5	40
4	100	5	2–5	<40
5	150	30	2–5	...
6	125	20	2–5	40
7	100	<2	3–6	5[d]
8	200[e]	20	2–5	50
9	75	40	1–2	...
10	125	10	3–5	<40
CPZ[f]	...	10	3–6	~50

[a] Comparisons were made using Wistar or Sprague–Dawley strain rats weighing from 150–250 g. [b] Approximate LD_{50}/72 hr obtained by intraperitoneal administration of the compounds to Wistar rats. [c] The effective dose was that which produced noticeable sedation and decreased spontaneous motor activity for at least 1 hr. [d] This compound, an azaspiranyl analog of chlorpromazine, was extremely potent. A dose of 10 mg/kg produced moderate to severe CNS depression, sedation, and tranquilization lasting for more than 48 hr. [e] As the citrate hydrate salt. All other compounds in the table were tested as their hydrochlorides. [f] CPZ = chlorpromazine.

The 10-azaspiranylalkylphenothiazines synthesized and screened in this study were prepared by reaction of the appropriate azaspirane[13] with 10-haloalkylphenothiazines or alkylation of 10-sodiophenothiazine with azaspiranylalkyl halides.[13] The isoindolinylalkylphenothiazine (Table I, **10**) was obtained by use of the isoindoline[16] secondary amine in lieu of an azaspirane. Compounds prepared and screened, together with appropriate physical and structural data, are listed in Table I.

Approximate LD_{50}/72 hr data were obtained by administering the compounds intraperitoneally to Wistar rats. The values are approximate because many of the animals that died on higher doses did so because of emaciation, since on these doses they were completely knocked down and could not eat or drink. In a few instances, in which they were fed by intubation, some survived.

The compounds were compared for CNS effects and relative potencies in rats.[13] These data are summarized in Table II. It can be seen that several of the azaspiranylalkylphenothiazines with unsubstituted phenothiazine nuclei were of the same order of potency (**1**–**4**) as chlorpromazine (CPZ), while the azaspiranyl analog of CPZ, **7**, was considerably more potent in rats. Compound **5**, in which the same azaspiranyl moiety as in **4** was attached to the 2 position of the trimethylene side chain, was rather ineffectual as a CNS depressant (compare promazine and promethazine). The large naphthalenespiropiperidine azaspiranyl system in **9** also produced a rather ineffectual CNS depressant.

The bicyclic isoindolinylalkylphenothiazine (**10**) was about as effective a CNS depressant as any of the bicyclic azaspiranyl structures containing 10–12 ring atoms and CPZ. However, it was the only member of this group which was observed to produce tremors on high dosage.

The most remarkable part of the observations was that none of the azaspiranylalkylphenothiazines produced tremors even at toxic levels. A characteristic of all other phenothiazine neuroleptics, and in particular the N′-substituted piperazinoalkyl derivatives, on average or high doses[11,17] is the production of tremor, extrapyramidal symptoms, or pseudo-Parkinsonism. Spasticity and akinesis, however, were observed at moderate to high doses.

(16) C. H. Grogan and L. M. Rice, *J. Med. Chem.*, **6**, 802 (1963).

(17) J. Delay and P. Deniker, *Rev. Can. Biol.*, **20**, 397 (1961).

Experimental Section[18]

10[3-(3-Azaspiro[5.5]undecan-3-yl)propyl]phenothiazine Hydrochloride (1).—10-(3-Chloropropyl)phenothiazine[19] (5 g, 0.018 mole) and 3-azaspiro[5.5]undecane[13] (5.6 g, 0.036 mole) were refluxed for 24 hr in 30 ml of toluene containing a few crystals of KI. The mixture was cooled, diluted with 2 vol of ether, and allowed to stand overnight at 5°. Precipitated **3-azaspiro[5.5]undecane hydrochloride**[13] was removed by filtration, washed with ether, and dried at 90°. It weighed 3.4 g, the theoretical amount. The filtrate was stripped at the water pump and then all material boiling up to 100° (0.2 mm) was removed at the vacuum pump and discarded. The residual oil was dissolved in 500 ml of absolute ether and saturated with HCl gas. The hydrochloride of the product was filtered, washed with ether, and dried at 90°. There was obtained 6 g (78%), mp 225–227 and 227–228°, after recrystallization from acetone–methanol–ether mixture.

10-[2-(8-Azaspiro[4.5]decan-8-yl)propyl]phenothiazine Hydrochloride (5).—10-(2-Bromopropyl)phenothiazine (mp 126–127°, 9.6 g, 0.03 mole), 8-azaspiro[4.5]decane[13] (8.4 g, 0.06 mole), and a few crystals of KI were refluxed for 30 hr in 100 ml of toluene. The cooled reaction mixture was diluted with 3 vol of ether and kept overnight at 5°. **8-Azaspiro[4.5]decane hydrobromide**[13] (5 g, theory 6.6 g) was removed by filtration and washed with ether. The filtrate and washings were stripped of solvent at the water pump until a viscous oil remained. All material boiling up to 100° (0.2 mm) was distilled; the residual oil was dissolved in 500 ml of ether and saturated with HCl gas. After filtering and drying the title compound, 8 g (65%) was obtained. It melted at 228–230° dec and at 232–234° dec after recrystallization from acetone–ether.

2-Chloro-10-[3-(3-azaspiro[5.5]undecan-3-yl)propyl]phenothiazine Hydrochloride (7).—2-Chlorophenothiazine (11.7 g, 0.05 mole) was dissolved in 50 ml of dimethylformamide and 2.6 g of a 55% suspension of NaH in mineral oil[20] was added. The mixture was heated to 50° and stirred until the evolution of hydrogen ceased. 3-(3-Chloropropyl)-3-azaspiro[5.5]undecane[13] (11.5 g, 0.05 mole) was added dropwise with stirring. The reaction mixture was maintained at 50° for 6 hr and poured into 500 ml of ice water. An oil separated which was washed by decantation several times with water. The purple oil that remained was dissolved in acetone, treated with decolorizing carbon, and filtered, and the solvent was evaporated. The residual light pink oil was dissolved in absolute ethanol and saturated with HCl gas, and several volumes of ether were added. An oil separated which slowly crystallized on slurrying with absolute ether. The product, 12 g (52%), melted at 205–206°, unchanged on recrystallization (slow) from acetone.

10-[3-(4-Methyl-4,7-epoxyhexahydroisoindolin-2-yl)propyl]-phenothiazine Hydrochloride (10).—A mixture of 10-(3-chloropropyl)phenothiazine (10 g, 0.036 mole), 4-methyl-4,7-epoxyhexahydroisoindoline[16] (11.1 g, 0.072 mole), and a few crystals of KI was refluxed for 2 days in 100 ml of toluene, and one-half of the toluene was distilled. The mixture was cooled, diluted with 3 vol of ether, and kept overnight at 5°. Precipitated **4-methyl-4,7-epoxyhexahydroisoindoline hydrochloride**[16] was removed by filtration (5.7 g, theory 6.8 g). The filtrate was evaporated until an oil remained. All material distillable up to 100° (0.2 mm) was removed from the residue and discarded. The residual oil was dissolved in ether and saturated with HCl gas to give the title compound, 9.6 g (62%), mp 124–127°. After two recrystallizations from ethylene chloride–ether, the material melted at 128–130° and softened around 114°.

(18) All melting points were taken in a Thomas–Hoover capillary type apparatus except the hydrate salt **9** which was taken on a Fisher-Johns block. Melting points are corrected. Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

(19) The commercial product is a dark, partly solid partly liquid mass. A specially purified material, pale yellow, mp 65–69°, prepared by repeated recrystallization from benzene–hexane and treated with decolorizing carbon, was used in these syntheses.

(20) Obtained from Metal Hydrides, Inc., Beverly, Mass.

Benzocyclobutene Derivatives. Oximes with Muscle Relaxant Characteristics[1]

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A number of 1-acylbenzocyclobutenes, their oximes, and several oxygen-substituted oximes were prepared and screened for potential mephenesin-like muscle relaxant activity. The compounds were obtained from a common precursor, 1-cyanobenzocyclobutene, which was made from *o*-chlorohydrocinnamonitrile by an improved method. The most effective material in the tests employed was the oxime of 1-acetylbenzocyclobutene, which was comparable in milligram potency to the comparative standard, chlorzoxazone.

To date, our study of the biological properties of compounds containing the bicyclo[4.2.0]octa-1,3,5-triene ring system has included the preparation of several 1-aminomethyl-[2] and various 1,1-disubstituted benzocyclobutenes.[3] Since skeletal muscle relaxant activity had been reported for the oximes of 2-acetyl-1,4-benzodioxane[4] and dicyclopropyl ketone,[5] compounds containing a carbonyl group adjacent to a cycloalkyl ring, a number of 1-acylbenzocyclobutenes and their oximes were made for screening as potential muscle relaxants. Several oxygen-substituted derivatives of one of the more interesting materials, 1-acetylbenzocyclobutene oxime, also were prepared. The synthesis and pharmacological evaluation of these compounds are described in the present report.

The ketones were made from 1-cyanobenzocyclobutene (**1**), which was prepared as shown in Scheme I. *o*-Chlorohydrocinnamonitrile (**2**), obtained in an overall yield of 53% from *o*-chlorobenzyl chloride and methyl cyanoacetate, was converted to **1** by a modification of the procedure of Bunnett and Skorcz.[6] This

(1) Presented in part before the Division of Medicinal Chemistry, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966.

(2) J. A. Skorcz and J. E. Robertson, *J. Med. Chem.*, **8**, 255 (1965).

(3) J. A. Skorcz and F. E. Kaminski, *ibid.*, **8**, 732 (1965).

(4) C. I. Judd, J. Freedman, and J. E. Robertson, Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p 22N.

(5) L. E. Blockus, G. M. Everett, and R. K. Richards, *Federation Proc.*, **17**, 350 (1958).

(6) J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962).