Spiranes. VII. Neuroleptics Derived from Azaspiranes[1]

CHARLES H. GROGAN,[2]

National Institutes of Health, Bethesda 14, Maryland

CHARLES F. GESCHICKTER,

Georgetown University Medical Center, Washington, D. C.

MEIER E. FREED,

Wyeth Laboratories, Inc., Radnor, Pennsylvania

AND LEONARD M. RICE

Howard University, Washington, D. C.

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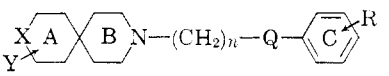
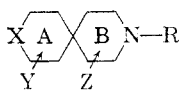
Azaspiranes with the hetero nitrogen atom in ring B in the 2- or 3-position have been prepared by reduction of the spiroimides. Derivatives of these typical secondary amines have been prepared by alkylation or acylation and studied pharmacologically. Permutation of structure



wherein AB is the azaspiranyl moiety, led to the discovery of a new class of potent neuroleptic compounds. When Q was —CO—, —CHOH—, —O—, or —S—, C was phenyl, and R was fluorine, members of this series were more potent than chlorpromazine, slightly less potent than haloperidol, and had a prolonged action, up to several days, in higher animals and man.

A broad program for the investigation of the chemical and pharmacological properties of heterocyclic compounds containing spiro carbon linkages at the ring junctions was undertaken several years ago. General synthetic methods for the preparation of compounds of this type, employing cyclic *gem*-carboxyacetic and -diacetic acids, and their esters and anhydrides, as starting materials, have been developed. These methods permit the synthesis of a wide variety of structural permutations of the basic structure I,[3] including variations of: (a) the size of rings A and B joined by the



I

spiro carbon atom, (b) the number of cycles in ring A, (c) the substituents Y and Z on rings A and B, (d) the additional heteroatom X included in ring A of the system (so far N, O, and S have been thus included), (e) the position of the N atom in ring B, and (f) the substituent R on ring B nitrogen. The values of R that can be obtained are practically limitless.

We have reported the synthesis and properties of a large series of compounds in which (a)–(e) were permuted as stated, and R was dialkylaminoalkyl or heterocyclicalkyl[4]; permutations (a)–(e) and R were alkyl, cycloalkyl, alkoxyalkyl, alkenyl, alkynyl, aryl, aralkyl and hydrazono[5]; diazaspiro compounds in which X was nitrogen with various substituents on N and X.[6,7] Recently we reported the extension of the synthetic methods to obtain three ring systems linked through two spiro carbon atoms.[8]

Chemistry.—The synthetic methods employed in the preparation of the compounds previously described (reaction of primary amines with cyclic *gem*-carboxyacetic or -diacetic acids, esters, or anhydrides followed by cyclization to the spiroimides) limited the values of R which could be obtained to those substituents containing primary amine groups and other functional groups which would not interfere with or be decomposed by the spiroimide formation process. Further, reduction of the spiroimides thus obtained (usually with lithium aluminum hydride) to the corresponding azaspiranes could not be carried out without altering other functional groups (*i.e.*, carbonyl, nitrilo, carboxy, ester, and certain halogen substituents thereon) in the R group.

We have accordingly prepared the previously unreported azaspiranes (R = H) with the hetero nitrogen atom in ring B in the 2- or 3-position.[9] Replacement of the hydrogen of these secondary amine azaspiranes by alkylation, acylation, etc., permitted us to obtain many values of R not accessible *via* the spiroimide intermediates. These new amines may be looked upon as 3- and 4-spiropyrrolidines and -piperidines, respec-

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(2) Author to whom inquiries should be addressed at the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Bethesda 14, Md.

(3) Throughout this paper and tables for convenience of discussion, the numbers 55, 56, 65, 66, 75, etc., will be used to designate the total number of atoms in rings A and B, respectively, counting the common spiro carbon atom in each ring for this purpose.

(4) L. M. Rice, C. F. Geschickter, and C. H. Grogan, *J. Med. Chem.*, **6**, 388 (1963).

(5) C. H. Grogan, C. F. Geschickter, and L. M. Rice, *ibid.*, **7**, 78 (1964).

(6) M. E. Freed, C. H. Grogan, and L. M. Rice, *J. Heterocyclic Chem.*, **1**, 125 (1964).

(7) Presented in part before the Division of Organic Chemistry, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964.

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

(9) Some 1-azaspiranes and 1-azaspirenes (derivatives) are reported in the literature. 1-Azaspiro[4.5]decane was obtained in poor yield by reductive cyclization of 1-nitro-1-(2-cyanoethyl)cyclohexane: (a) A. N. Kost, A. V. Kamernitskii, and S. M. Gurvich, *Vestnik. Mosk. Univ.*, **9**, *Ser. Fiz-Mat. i Estestven Nauk.*, **No. 6**, 115 (1954); *Chem. Abstr.*, **49**, 15856 (1954); (b) R. B. Moffett, *J. Am. Chem. Soc.*, **79**, 3186 (1957). Derivatives of 1-azaspiro[4.5]dec-2-ene and 1-azaspiro[4.4]non-2-ene have been reported: (c) R. J. S. Beer, W. T. Gradwell, and W. J. Oates, *J. Chem. Soc.*, 4693 (1958).

tively; and indeed many of their reactions were similar to these monocycles.

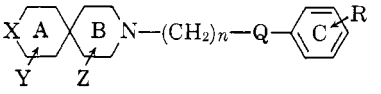
The spiroimides were obtained from the corresponding cyclic *gem*-carboxyacetic and -diacetic acids, esters, or anhydrides and concentrated aqueous NH_3 followed by cyclization at 160–200°. Although most of the imides prepared had been reported previously in the literature, they are listed in Table I (part A), reference to the amines prepared therefrom, and physical constants of the imides we obtained and employed in our syntheses.[10]

On theoretical grounds the elimination of one asymmetric center from the cyclohexane ring[10a-m] by *gem* substitution of the diacetic group (leaving the other asymmetric center intact, Table I, compounds **6, 8–11**) should still permit the existence of two isomeric boat and chair forms of these acids as well as of their imides. In all cases included in the table only one acid and one imide (or a preponderance of one form) was obtained.

In the case of compound **2** (Table I), one isomeric form also predominated. Our material (Table I, **13**) was derived from *trans*-β-decalone and the imide is probably all *trans* as indicated by the small difference from the literature (Table I, ref. *l*) m.p. of 201° for this isomer and the 15–20° depression on admixture with the *cis* isomer.

The imides listed in Table I, part A, were reduced to the azaspiranes (Table I, part B) with lithium aluminum hydride in anhydrous ether. In general those amines in which ring B was piperidine were obtained in better yield on the scale employed (0.05 to 0.3 *M*) than were those in which ring B was pyrrolidine. The sharpness of the original melting point, and little or no change on recrystallization, of the picrates of these amines again indicated that only one isomeric form was obtained.

Early in our investigations of derivatives of these amines it was found that the 3-(*p*-fluorobenzoyl)propyl N-substituent resulted in compounds with potent CNS depressant properties similar to those observed with the phenothiazine-derived tranquilizer, chlorpromazine. The work reported herein, aside from the synthesis of the azaspiranes, deals largely with the synthesis and pharmacology of compounds derived from permutations of the structure II. This structure was permuted as

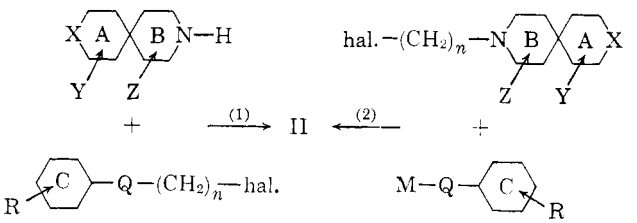


II

follows: number of atoms in ring A, position of the N atom, and number of atoms in ring B; substituents Y on ring A; values of *n* from 1 to 7; values of Q including $-CH_2-$, $-CO-$, $-CHOH-$, $-O-$, $-S-$, $-SO_2-$; ring C was phenyl or thenyl; values of R included H, F, Br, Cl, alkyl, trifluoromethyl, and alkoxy. In addition, ring A was opened to study the effects of 4,4-disubstituted piperidines or was eliminated altogether to leave simply piperidine or morpholine.

Various compounds prepared, together with intermediate N-substituted azaspiranylalkyl acids, esters, alcohols, halides, nitriles and amines, are listed in Table II. The compounds were obtained by two general routes as shown in Scheme I.

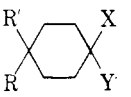
SCHEME I



Method 1 consisted of treating the azaspirane with the aralkyl, aryloxyalkyl, or aroylalkyl halide in an inert solvent such as toluene. Method 2 employed the azaspiranylalkyl halide and the alkali metal salt of the phenol, thiophenol, or arylsulfinate, usually in ethanol as reaction medium. The general methods, and variants thereof, are illustrated by specific examples in the Experimental section. Again, in general, the yields of compounds formed by alkylation of the free azaspiranes in which ring B was piperidine were better than those obtained in cases where ring B was pyrrolidine, and the reactions were cleaner.

An interesting chemical observation, which may be of biological significance with this type of structure, was the relatively high lability of the fluorine atom substituted on the aromatic ring of 4-chloro-4′-fluorobutyrophenone. A search for the cause of the disparity between the yields of 4-substituted azaspiranylbutyrophenones obtained when the nitrogen atom in ring B was in the 1- or 2-position (pyrrolidines) or the 3-position (piperidines) brought about this conclusion. With the pyrrolidines (and to a lesser extent with the piperidines) there was always a relatively large high-boiling residue which solidified to a hard resin on cool-

(10) A considerable controversy, and much work as a result thereof, is recorded in the literature concerning the number of isomers obtainable for acids of the structure



derived from cyclohexane, wherein X and Y are carboxyl and acetic groups and R and R′ are different substituents. On theoretical grounds multiplanarity of the cyclohexane ring should contribute two isomers in addition to the *cis* and *trans* configurations. Qudrat-i-Khuda and co-workers[10a-d] reported the isolation of four isomers of 3- and 4-methylcyclohexane-1-carboxyl-1-acetic acids along with their anhydrides, imides, and anils. These findings were disputed by Desai, *et al.*,[10e-k] who were able to isolate only the *cis* and *trans* isomers of 3- and 4-methylcyclohexane-1-carboxy-1-acetic acids, their anhydrides, and imides, as well as only one form of 3,3-dimethylcyclohexane-1-carboxy-1-acetic acid.[10f] Goldschmidt and Gräfinger[10l] isolated only two isomeric acids and imides of 4-methylcyclohexane-1-carboxy-1-acetic acid and showed by melting point studies that the other "multiplanar ring isomers" of Qudrat-i-Khuda, *et al.*, were 1:1 and 4:1 mixtures of the *cis* and *trans* isomers. The failure to obtain more than one isomeric *gem*-carboxyacetic acid of the 3,3-dimethyl-[10f] or the 4,4-dimethyl-substituted[10m] cyclohexane ring, as well as the fact that the transformation energy is very small,[10j,m] mitigates against the isolability of the boat and chair forms. However, this does not eliminate the possibility that other substituents on the ring might alter the transformation energy between the boat and chair forms, or hinder interconversion sufficiently to permit the isolation of four isomers in some cases. (a) M. Qudrat-i-Khuda, *J. Indian Chem. Soc.*, **8**, 277 (1931); (b) M. Qudrat-i-Khuda, and A. Mukherji, *ibid.*, **15**, 462 (1938); (c) M. Qudrat-i-Khuda, *Nature*, **132**, 210 (1933); (d) M. Qudrat-i-Khuda, *ibid.*, **136**, 301 (1935); (e) R. D. Desai, *J. Chem. Soc.*, 1047, 1065 (1932); (f) R. D. Desai and R. F. Hunter, *Nature*, **136**, 608 (1935); (g) R. D. Desai, R. F. Hunter, G. Khan, and G. S. Saharia, *J. Chem. Soc.*, 416 (1936); (h) M. W. Bukhsh, R. D. Desai, R. F. Hunter, and M. Hussain, *ibid.*, 1159 (1936); (i) R. D. Desai, M. O. Farooq, and R. F. Hunter, *ibid.*, 1162 (1936); (j) R. D. Desai, R. F. Hunter, and G. S. Saharia, *ibid.*, 84 (1939); (k) R. D. Desai, R. F. Hunter, and G. S. Saharia, *Proc. Indian Acad. Sci.*, **14A**, 516 (1941); (l) S. Goldschmidt and G. Gräfinger, *Ber.*, **68**, 279 (1935); (m) R. F. Miller and R. Adams, *J. Am. Chem. Soc.*, **58**, 787 (1936).

ing. Analysis of the forerun (fraction 10° below up to the main fraction) and a flash distillate of part of the residue gave fractions, boiling far above either reactant, containing little or no fluorine. This led us to suspect defluorination as a major side reaction.

In the preparation of compound **9**, Table II, on a larger scale for clinical trials, v.p.c. consistently showed a 2–4% content of a nonfluorine-containing material distilling with the main fraction. The use of a hindered tertiary amine (such as diisopropylethylamine) as an acid scavenger and to conserve azaspirane decreased resin formation somewhat. The relative ease of defluorination of 4-chloro-4′-fluorobutyrophenone by other secondary amines was verified and is being further investigated.

Pharmacology.—Compounds were screened grossly[9] during toxicity-range studies in Wistar rats by observation over a period of 72 hr. for general behavior,[5] autonomic effects (salivation, vomiting, urination, defecation), and reflex and motor effects. The effects seen at small doses (< 5 mg./kg.), general depression, sedation, ataxia, decreased muscle tone, decreased spontaneous motor activity, for the more potent compounds resembled closely those seen with phenothiazine-derived tranquilizers. There was also a marked blanching of the paws and eyes which indicated a lowering of blood pressure. At intermediate doses (5–15 mg./kg.), flaccidity, disturbance of autonomic function, catalepsy, and deep sedation were observed. At doses approaching the toxic range, animals were knocked down for several days, experienced clonic and tonic convulsions, marked autonomic disturbances, catalepsy, and were unable to eat or drink. Compounds which showed sufficient activity in the preliminary screen were run through a battery of CNS screens and compared with chlorpromazine and haloperidol,[11a–k] phenothiazine, and butyrophenone-type tranquilizers, respectively.[12] For a comparison of haloperidol and chlorpromazine, see ref. 11d; for comparisons among the various other butyrophenone derivatives of Janssen (haloperidol, triperidol, dipiperon, luvatren, haloperidide, haloanison), see ref. 11h; and for a general review, see ref. 11k.

Antimorphine and antitremorine activity was determined in mice at various doses of test drug administered *p.o.* followed by i.p. administration of morphine sulfate or Tremorine 1 hr. later. Antimorphine effects were expressed as the average *p.o.* dose which decreased the incidence of circling and Straub tail in 50% of the animals.

Spontaneous motor activity was determined in mice at various dosage levels of test and comparison drugs, administered i.p. or *p.o.*, in photoelectric activity cages.

Forced motor activity was determined in mice at various times after administration of test and comparison drugs by the rotating horizontal bar (2.54-cm. diameter, 30 r.p.m.) method.

Convulsant Activity Potentiation.—Potentiation of the convulsant activity produced by a minimal corneal electroshock potential (in mice such that 30% of controls convulsed at this potential) was determined at various *p.o.* doses followed by shocking 1 hr. later.

Behavioral Changes. A. Conditioned avoidance behavior[13] was determined in rats conditioned to avoid a shock from a charged grid by running on a treadmill. This was a cyclic procedure whereby stepping off the treadmill onto the grid caused a 5-sec. audible signal followed by charging of the grid. Various time parameters related to shock time, number of shocks, and times on grid with and without shock were compared.

B. Approach behavior[13] determined the effect of drugs on hungry rats obtaining food while walking on a constant-speed treadmill. The amount of food obtained, time on tread, and times stepped off tread were compared.

C. General Observation of Effects.—The time of onset and duration of action, general behavior, reflex and motor effects, autonomic effects, sedation, catalepsy were studied in cats (5–10 mg./kg.) and Rhesus monkeys (0.15–2.0 mg./kg.).

Cardiovascular Effects. A.—Blood pressure and heart rate measurements were made on anesthetized cats and on unanesthetized dogs by femoral artery puncture or with a transducer pickup.

B.—Effects on blood pressure, heart rate, myocardial contractile force (by a strain-gauge arch sutured to the right ventricle) were determined in pentobarbital-anesthetized, artificially respired, open-chest dogs.

C.—Hind leg perfusion studies (pumping blood from proximal to distal cannulae inserted into the abdominal aorta) were performed in dogs. Changes in perfusion pressure reflected changes in vascular resistance in the hind quarters. Effects of test drugs on responses to administered epinephrine, norepinephrine, glyceryl trinitrate, acetyl choline (i.a.), and norepinephrine (i.v.) were determined.

Antiserotonin and antihistamine activity were determined on the isolated guinea pig ileum in Tyrode's solution.

Electroencephalographic Studies.—Acute, subchronic, and chronic studies were made in cats primarily to ascertain the extent and specificity of limbic-system activation as compared to generalized cortical activation at convulsive doses and to determine the dose–response relations required.

Antiinflammatory activity was determined in rats by either the cotton pellet granuloma pouch or egg white inflammation-producing techniques.[5] On a comparative scale, aspirin had values of 10–20% reduction in inflammation at therapeutic levels, 200–400 mg./kg.

Results and Discussion

The results of pharmacological screening studies are summarized in Table III. From these data it is ap-

(11) (a) P. A. J. Janssen, C. van de Westeringh, A. H. M. Jageneau, P. J. A. Demoen, B. K. F. Hermann, G. H. P. Van Daele, K. H. L. Schellekens, C. A. M. Van der Eycken, and C. J. E. Niemegeers, *J. Med. Pharm. Chem.*, **1**, 281 (1959); (b) J. Delay, P. Deniker, and M. Perier, *Compt. rend. soc. biol.*, **154**, 1177 (1960); (c) C. J. E. Niemegeers and P. A. J. Janssen, *J. Pharm. Pharmacol.*, **12**, 744 (1960); (d) P. A. J. Janssen, C. J. E. Niemegeers, and K. H. L. Schellekens, *Arzneimittel-Forsch.*, **10**, 955 (1960); (e) W. K. A. Schaper, A. H. M. Jageneau, H. Huygens, and P. A. J. Janssen, *Med. Exptl.*, **3**, 169 (1960); (f) P. J. A. Demoen, *J. Pharm. Sci.*, **50**, 350 (1961); (g) P. A. J. Janssen and C. J. E. Niemegeers, *Arzneimittel-Forsch.*, **11**, 1037 (1961); (h) P. A. J. Janssen, *ibid.*, **11**, 819, 932 (1961); (i) P. A. J. Janssen, C. J. E. Niemegeers, K. H. L. Schellekens, F. J. Verbruggen and J. M. Van Nueten, *ibid.*, **13**, 205 (1963); (j) J. R. Boissier and J. Pagny, *Therapie*, **15**, 479 (1960); (k) J. Collard, *Rec. Cas. Biol.*, **20**, 465 (1961).

(12) Compounds of interest were run through the CNS screens of Wyeth Laboratories, Inc., Radnor, Pa. We are grateful to Drs. M. J. Hosko and M. J. Gluckman for a report of their findings in these screens

(13) M. J. Gluckman, *The Pharmacologist*, **3**, 76 (1961).

TABLE I. PART A, SPIROIMIDES

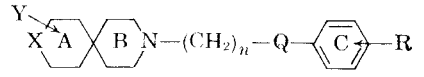
No.	Ring system, Y-AB	M.p., °C.	Formula	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
1	55	120–122[a]	$C_8H_{11}NO_2$	62.73	7.24	9.14	62.58	7.06	9.11
2	7-Me–55	96–97[b]	$C_9H_{13}NO_2$	64.65	7.84	8.38	64.88	8.13	8.40
3	65	144–145[c]	$C_9H_{13}NO_2$	64.65	7.84	8.38	64.92	8.05	8.81
4	75	114–115[d]	$C_{10}H_{15}NO_2$	66.27	8.34	7.73	66.68	8.39	7.82
5	56	152–153[e]	$C_9H_{13}NO_2$	64.65	7.84	8.38	64.90	8.01	8.67
6	8-Me–56	135.5–136.5[f]	$C_{10}H_{15}NO_2$	66.27	8.34	7.73	66.75	8.47	7.60
7	66	168–169[g]	$C_{10}H_{15}NO_2$	66.27	8.34	7.73	66.54	8.33	7.76
8	8-Me–66	153–154[h]	$C_{11}H_{17}NO_2$	67.66	8.78	7.17	67.48	9.07	7.00
9	9-Me–66	163–164[i]	$C_{11}H_{17}NO_2$	67.66	8.78	7.17	67.87	9.03	7.14
10	9-*t*-Butyl–66	223–224	$C_{14}H_{23}NO_2$	70.85	9.77	5.90	70.89	9.83	5.96
11	9-Cyclohexyl–66	189–190	$C_{16}H_{25}NO_2$	72.96	9.57	5.32	73.23	9.67	5.36
12	76	177–178[j]	$C_{11}H_{17}NO_2$	67.66	8.78	7.17	67.53	8.86	7.44
13	10-6[k]	197–199[l]	$C_{14}H_{21}NO_2$	71.45	9.00	5.95	71.30	8.87	6.04
14[m]	7,9-Dimethyl–8-oxa–65	184–185	$C_{10}H_{15}NO_3$	60.90	7.66	7.10	60.62	7.71	7.31

PART B, SPIROAMINES

No.	Ring system	B.p., °C. (mm.)	Yield, %	Formula	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
1	55	70 (14)	80	$C_8H_{15}N$[n]	76.75	12.08	11.19	77.00	12.06	11.22
2	7-Me–55	71–73 (12)	87	$C_9H_{17}N$[o]	77.63	12.31	10.06	77.44	12.15	10.27
3	65	89–92 (20)	55	$C_9H_{17}N$[p]	77.63	12.31	10.06	77.72	12.49	10.17
4	75	106–110 (15)	68	$C_{10}H_{19}N$[q]	78.36	12.50	9.14	78.72	12.60	9.21
5	56	83–86 (16)	80	$C_9H_{17}N$[r]	77.63	12.31	10.06	77.44	12.21	10.08
6	8-Me–56	90–93 (14)	71	$C_{10}H_{19}N$[s]	78.36	12.50	9.14	78.14	12.56	9.04
7	66	114 (23), 110–112 (10)	79	$C_{10}H_{19}N$[t]	78.36	12.50	9.14	78.63	12.56	9.19
8	8-Me–66	120–123 (20)	88	$C_{11}H_{21}N$[u]	78.97	12.65	8.37	78.92	12.88	8.32
9	9-Me–66	70–74 (0.75)	75	$C_{11}H_{21}N$[v]	78.97	12.65	8.37	79.23	12.82	8.47
10	9-*t* Butyl–66	138 (4.5)	84	$C_{14}H_{27}N$[w]	80.31	13.00	6.69	79.95	12.75	6.61
11	9-Cyclohexyl–66	120–130 (0.2)	78	$C_{16}H_{29}N$[x]	81.63	12.42	5.95	81.67	12.35	5.85
12	76	138–140 (27)	80	$C_{11}H_{21}N$[y]	78.97	12.65	8.37	78.82	12.85	8.46
13	10-6[k]	103–105 (0.6)	67	$C_{14}H_{25}N$[z]	81.09	12.15	6.76	81.17	12.24	7.10
14	7,9-Dimethyl–8-oxa–65	93–95 (10)	78	$C_{10}H_{19}NO$[aa]	70.96	11.31	8.28	71.16	11.36	8.00

[a] S. S. G. Sircar [*J. Chem. Soc.*, 1252 (1927)] gives m.p. 124°. [b] R. D. Desai [*ibid.*, 1216 (1931)] gives m.p. 98°. [c] Lit.[a] m.p. 145°; S. Nakamura and M. Aimiya [Japanese Patent 7574 (October 19, 1955)] give m.p. 147°; F. Dickens, L. Horton, and J. F. Thorpe [*J. Chem. Soc.*, **125,** 1831 (1924)] give m.p. 145°. [d] F. Dickens, L. Horton, and J. F. Thorpe [*ibid.*, **125,** 1830 (1924)] give m.p. 116°. [e] G. A. R. Kon and J. F. Thorpe [*ibid.*, **115,** 686 (1919)] give m.p. 153°; S. S. G. Sircar [*ibid.*, 600 (1927)] gives m.p. 153–154°. [f] Lit.[b] m.p. 133–134°. [g] Sircar[e] gives m.p. 169°; F. B. Thole and J. F. Thorpe [*ibid.*, **99,** 422 (1911); *Proc. Chem. Soc.*, 42 (1911)] give m.p. 168°. [h] J. F. Thorpe and A. S. Wood [*J. Chem. Soc.*, **103,** 1586 (1913)] give m.p. 155°. [i] Thorpe and Wood[h] give m.p. 162°. [j] J. N. E. Day, G. A. R. Kon, and A. Stevenson [*ibid.*, **117,** 639 (1920)] give m.p. 177–178.5°. [k] *trans*-Decalin-2,4′-piperidine. [l] K. A. N. Rao [*J. Chem. Soc.*, 1954 (1929)] gives *trans* isomer, m.p. 201°; *cis* isomer, m.p. 205°; mixed *cis–trans*, m.p. 180–185°. [m] While there are other references to compounds **5, 7,** and **12** in the literature, dealing largely with pharmacological properties, no physical constants or preparative data are given therein. Nicholas Proprietary Ltd., British Patent 808,269 (January 28, 1959); *Chem. Abstr.*, **53,** P10670*g*; T. C. Somers, *Nature*, **178,** 996 (1957); P. G. Marshall and D. K. Vallance, *J. Pharm. Pharmacol.*, **6,** 740 (1954). [n] Picrate, m.p. 161.5–162°, diamond-shaped prisms from methanol. *Anal.* Calcd. for $C_{14}H_{18}N_4O_7$: N, 15.81. Found: 15.69. Hydrochloride, very hydroscopic. Hydrobromide, m.p. 99–100° from ethyl acetate. *Anal.* Calcd. for $C_8H_{16}BrN$: Br, 38.77. Found: Br, 38.53. [o] Picrate, m.p. 124–125° from ethanol (picric acid melts at 122–123°; an admixture with this picrate melted at 88–90°). *Anal.* Calcd. for $C_{15}H_{20}N_4O_7$: N, 15.21. Found: N, 15.21. [p] Picrate, m.p. 148–148.5° from ethanol. *Anal.* Calcd. for $C_{15}H_{20}N_4O_7$: N, 15.21. Found: N, 15.36. Hydrobromide, m.p. 145–145.5 from ethyl acetate. *Anal.* Calcd. for $C_9H_{18}BrN$: Br, 36.30. Found: Br, 36.10. [q] Picrate, m.p. 145–146° from ethanol. *Anal.* Calcd. for $C_{16}H_{22}N_4O_7$: N, 14.65. Found: N, 14.89. [r] Base is carbonated rapidly in air. Picrate, m.p. 208–209° from methanol. *Anal.* Calcd. for $C_{15}H_{20}N_4O_7$: N, 15.21. Found: N, 15.39. Hydrochloride, m.p. 233–235° from ethanol. *Anal.* Calcd. for $C_9H_{18}ClN$: Cl, 20.18. Found: Cl, 20.01. Hydrobromide, m.p. 196–197° from acetone. *Anal.* Calcd. for $C_9H_{18}BrN$: Br, 36.30. Found: Br, 36.27. [s] Picrate, m.p. 168–169° from ethanol. *Anal.* Calcd. for $C_{16}H_{22}N_4O_7$: N, 14.65. Found: N, 14.75. Hydrochloride, m.p. 237–238° from ethanol. *Anal.* Calcd. or $C_{10}H_{20}ClN$: Cl, 18.69. Found: Cl, 18.39. [t] Picrate, m.p. 193–194° from ethanol. *Anal.* Calcd. for $C_{16}H_{22}N_4O_7$: N, 14.65. Found: N, 14.53. Hydrochloride, m.p. 239–240° from ethanol. *Anal.* Calcd. for $C_{10}H_{20}ClN$: Cl, 18.69. Found: Cl, 18.53. Hydrobromide, m.p. 200–201° from ethanol. *Anal.* Calcd. for $C_{10}H_{20}BrN$: Br, 34.12. Found: Br, 33.81. [u] Picrate, m.p. 183–184° from ethanol. *Anal.* Calcd. for $C_{17}H_{24}N_4O_7$: N, 14.13. Found: N, 13.82. Hydrochloride, m.p. 260–260.5° from methanol–acetone. *Anal.* Calcd. for $C_{11}H_{22}ClN$: Cl, 17.40. Found: 17.23. Hydrobromide, m.p. 247–248° from acetone. *Anal.* Calcd. for $C_{11}H_{22}BrN$: Br, 32.20. Found: Br, 32.56. [v] Picrate, m.p. 179–180° from ethanol. *Anal.* Calcd. for $C_{17}H_{24}N_4O_7$: N, 14.13. Found: N, 13.92. Hydrochloride, m.p. 259–261° from ethanol. *Anal.* Calcd. for $C_{11}H_{22}ClN$: Cl, 17.40. Found: Cl, 17.35. [w] Hydrochloride, m.p. 308–310° dec. from ethanol. *Anal.* Calcd. for $C_{14}H_{28}ClN$: Cl, 14.42. Found: Cl, 14.56. Hydrobromide, m.p. 285–286° from methanol–acetone. *Anal.* Calcd. for $C_{14}H_{28}BrN$: Br, 27.53. Found: Br, 27.67. Free amine, m.p. 83–83.3° from ligroin or acetone–water. [x] Picrate, m.p. 194–195° from ethanol. *Anal.* Calcd. for $C_{22}H_{32}N_4O_7$: C, 56.88; H, 6.94; N, 12.06. Found: C, 57.09; H, 7.17; N, 11.72. Hydrochloride, m.p. 313–314° dec. from ethanol. *Anal.* Calcd. for $C_{16}H_{30}ClN$: Cl, 13.04. Found: Cl, 13.05. Free amine, m.p. 63–64° from ligroin or 30–60° petroleum ether. [y] Picrate, m.p. 181–182° from ethanol. *Anal.* Calcd. for $C_{17}H_{24}N_4O_7$: N, 14.13. Found: N, 14.30. Hydrochloride, m.p. 291–292° dec. from ethanol. *Anal.* Calcd. for $C_{11}H_{22}ClN$: Cl, 17.40. Found: Cl, 17.43. Hydrobromide, m.p. 262–263° from methanol–acetone. *Anal.* Calcd. for $C_{11}H_{22}BrN$: Br, 32.20. Found: Br, 32.42. [z] Hydrochloride, m.p. 273–274° dec. from ethanol. *Anal.* Calcd. for $C_{14}H_{26}ClN$: Cl, 14.54. Found: Cl, 14.42. Hydrobromide, m.p. 258–259° from methanol–ethyl acetate. *Anal.* Calcd. for $C_{14}H_{26}BrN$: Br, 27.72. Found: Br, 27.90. [aa] Picrate, m.p. 180–181° from ethanol, very slow even on adding an equal volume of ether. *Anal.* Calcd. for $C_{16}H_{22}N_4O_8$: N, 14.06. Found: N, 13.90. Hydrochloride, m.p. 152–153° from acetone. *Anal.* Calcd. for $C_{10}H_{20}ClNO$: Cl, 17.23. Found: Cl, 16.99. Hydrobromide, m.p. 157.5–158.5 from ethyl acetate. *Anal.* Calcd. for $C_{10}H_{20}BrNO$: Br, 31.94. Found: Br, 31.73.

TABLE II



No.	Ring system, Y–AB	n	Q	R–C	B.p., °C. (mm.)	Yield, %	Formula	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
1	55	3[a]	–CO–	*p*-BrC_6H_4	170–180 (0.15)	87	$C_{18}H_{24}BrNO$	...	...	...	...	...	...
2	7-Me-55	3	–CO–	*p*-FC_6H_4	135–145 (0.26)	43	$C_{19}H_{26}FNO$	75.21	8.64	4.62	74.98	8.53	4.47
3	65	3	–CO–	*p*-FC_6H_4	135–140 (0.15)	59	$C_{19}H_{26}FNO$[b]	75.21	8.64	6.26[c]	75.39	8.87	5.93[c]
4	75	3	–CO–	*p*-FC_6H_4	155–165 (0.2)	38	$C_{20}H_{28}FNO$[d]	75.67	8.89	5.99[c]	75.94	9.23	6.24[c]
5	56	3	–CO–	*p*-FC_6H_4	143–146 (0.17)	72	$C_{19}H_{26}FNO$[e]	75.21	8.64	6.26[c]	75.47	8.82	6.58[c]
6	8-Me–56	3	–CO–	*p*-FC_6H_4	145–155 (0.13)	76	$C_{20}H_{28}FNO$[f]	75.67	8.89	5.99[c]	75.78	9.01	5.80[c]
7	65	3	–CO–	*p*-FC_6H_4	150–160 (0.35)	61	$C_{19}H_{26}FNO$[g]	75.21	8.64	6.26[c]	74.92	8.93	6.06[c]
8	66	3	–CO–	Phenyl	...	58	$C_{20}H_{30}ClNO$[h]	71.51	9.00	4.17	71.28	9.22	4.31
9	66	3	–CO–	*p*-FC_6H_4	...	49	$C_{20}H_{29}ClFNO$[i]	67.87	8.26	..	67.59	8.42	..
10	8-Me–66	3	–CO–	*p*-FC_6H_4	150–160 (0.2)	87	$C_{21}H_{30}FNO$[j]	76.09	9.12	5.73[c]	75.84	9.09	5.58[c]
11	9-*t*-Butyl-66	3	–CO–	*p*-FC_6H_4	170–180 (0.2)	80	$C_{24}H_{36}FNO$[k]	77.17	9.71	5.09[c]	77.47	9.94	4.93[c]
12	66	3	–CO–	*p*-$MeOC_6H_4$	...	77	$C_{21}H_{32}ClNO_2$[l]	...	...	...	...	...	..
13	9-Me–66	3	–CO–	*p*-FC_6H_4	155–165 (0.15)	75	$C_{21}H_{30}FNO$[m]	76.09	9.12	5.73[c]	76.39	9.33	5.55[c]
14	9-Cyclohexyl-66	3	–CO–	*p*-FC_6H_4	...	85	$C_{26}H_{39}ClFNO$[n]	...	...	...	...	...	...
15	66	3	–CHOH–	*p*-FC_6H_4	...	...	$C_{20}H_{31}ClFNO$[o]	67.49	8.78	3.94	67.74	9.01	4.00
16	9-Me-9-aza–66	3	–CO–	*p*-FC_6H_4	185–190 (0.1)	67	$C_{20}H_{31}Cl_2FN_2O$[p]	...	...	6.65	...	...	6.72
17	66	1	–CO–	*o,o'*-Xylidinyl	...	80	$C_{20}H_{31}ClN_2O$[q]	68.45	8.90	7.98	68.24	9.13	8.20
18	66	2	–OCO–	*p*-$NH_2C_6H_4$	...	70	$C_{19}H_{30}Cl_2N_2O_2$[r]	58.61	7.77	7.20	58.59	7.95	7.48
19	66	*s*	*s*	*s*	...	56	$C_{23}H_{29}Cl_2N$[s]	70.76	7.49	3.59	70.58	7.26	3.42
20	*l*	3	–CO–	*p*-FC_6H_4	...	Quant.	$C_{17}H_{14}FNO_4S$	58.78	4.06	5.47[c]	58.70	4.17	5.50[c]
21	66	3	–CO–	2-Thienyl	160–170 (0.2)	86	$C_{18}H_{27}NOS$	70.77	8.90	10.50[c]	71.08	9.18	10.40[c]
22	76	3	–CO–	*p*-FC_6H_4	170–180 (0.2)	77	$C_{21}H_{30}FNO$[t]	76.09	9.12	5.73[c]	75.82	9.10	5.90[c]
23	10-6[u]	3	–CO–	*p*-FC_6H_4	...	88	$C_{24}H_{33}ClFNO$[v]	...	...	...	...	...	...
24	7,9-Di-Me-8-Oxa-65	3	–CO–	*p*-FC_6H_4	130–140 (0.1)	72	$C_{20}H_{28}FNO_2$[w]	72.04	8.46	5.70[c]	71.77	8.58	5.79[c]
25	Piperidine	3	–CO–	*p*-FC_6H_4	101–106 (0.12)	83	$C_{15}H_{20}FNO$[x]	...	...	...	...	...	...
26	4,4-Di-Me–piperidine	3	–CO–	*p*-FC_6H_4	...	..	$C_{17}H_{25}ClFNO$[y,z]	65.06	8.03	4.46	64.86	8.12	4.32
27	4-Me-4-Pr–piperidine	3	–CO–	*p*-FC_6H_4	..	..	$C_{19}H_{29}ClFNO$[y,aa]	66.74	8.55	4.19	66.47	8.63	4.32
28	4,4-Di-Et–piperidine	3	–CO–	*p*-FC_6H_4	..	..	$C_{19}H_{29}ClFNO$[z]	66.74	8.55	4.19	66.53	8.67	4.24
29	Morpholine	3	–CO–	*p*-FC_6H_4	120–125 (0.1)	81	$C_{14}H_{19}ClFNO_2$[z,ab]	58.43	6.65	4.87	58.38	6.78	4.59
30	55	3	–O–	*p*-FC_6H_4	115–120 (0.24)	75	$C_{17}H_{24}FNO$[ac]	73.61	8.72	5.05	73.71	9.04	4.79
31	65	3	–O–	*p*-FC_6H_4	...	..	$C_{18}H_{27}ClFNO$[z]	...	...	...	...	...	.
32	65	3	–O–	*p*-FC_6H_4	...	..	$C_{18}H_{27}ClFNO$[z,ac]	...	...	...	...	...	.

No.	Ring system, Y–AB	n	Q	R–C	B.p., °C. (mm.)	Yield, %	Formula	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
33	56	3	–O–	*p*-FC_6H_4	...	..	$C_{18}H_{27}ClFNO^{hh}$	...	...	...	...	...	...
34	66	2	–O–	*p*-FC_6H_4	135–145 (0.25)	92	$C_{18}H_{26}FNO^{ii}$	74.19	8.99	6.52[c]	73.88	8.76	6.43[c]
35	66	3	–O–	*o*-FC_6H_4	135–145 (0.27)	87	$C_{19}H_{28}FNO^{ij}$	74.71	9.24	4.59	74.71	9.31	4.92
36	66	3	–O–	*m*-FC_6H_4	140–150 (0.25)	90	$C_{19}H_{28}FNO^{kk}$	74.71	9.24	4.59	74.77	9.45	4.77
37	66	3	–O–	*p*-FC_6H_4	145–155 (0.27)	87	$C_{19}H_{28}FNO^{ll}$	74.71	9.24	4.59	74.71	8.90	4.57
38	66	3	–O–	*m*-$F_3CC_6H_4$	130–140 (0.2)	79	$C_{20}H_{28}F_3NO^{mm}$	67.58	7.94	16.04[c]	67.43	7.86	15.75[c]
39	8-Me–66	3	–O–	*p*-FC_6H_4	...	..	$C_{20}H_{31}ClFNO^{nn}$	...	...	...	...	...	...
40	9-*t*-Butyl–66	3	–O–	*p*-FC_6H_4	...	..	$C_{23}H_{37}ClFNO^{oo}$	...	...	...	...	...	...
41	66	3	–O–	*p*-ClC_6H_4	158–165 (0.08)	78	$C_{19}H_{29}Cl_2NO^{pp}$	...	...	...	...	...	...
42	66	3	–O–	*p*-$MeOC_6H_4$	155–165 (0.075)	82	$C_{20}H_{32}ClNO_2^{qq}$	...	...	...	...	...	...
43	66	3	–S–	*p*-FC_6H_4	130–136 (0.3)	71	$C_{19}H_{28}FNS^{rr}$	70.98	8.78	4.36	70.69	8.68	4.24
44	66	3	$–SO_2–$	C_6H_5	...	..	$C_{19}H_{30}ClNO_2S^{ss}$	61.35	8.10	3.77	61.08	7.92	3.68
45	66	3	$–SO_2–$	*p*-MeC_6H_4	...	..	$C_{20}H_{32}ClNO_2S^{tt}$	62.23	8.36	3.63	62.07	8.14	3.45
46	66	3	$–SO_2–$	*p*-FC_6H_4	...	..	$C_{19}H_{29}ClFNO_2S^{uu}$	58.53	7.50	3.59	58.82	7.68	3.65
47	66	4	–O–	*p*-FC_6H_4	150–160 (0.27)	83	$C_{20}H_{30}FNO^{vv}$	75.19	9.47	4.38	75.11	9.37	4.55
48	66	5	–O–	*p*-FC_6H_4	150–160 (0.24)	71	$C_{21}H_{32}FNO^{ww}$	75.63	9.67	4.20	75.79	9.83	4.45
49	76	3	–O–	*p*-FC_6H_4	...	..	$C_{20}H_{31}ClFNO^{xx}$	...	...	...	...	...	...
50	10-6[r]	3	–O–	*p*-FC_6H_4	...	..	$C_{23}H_{25}ClFNO^{yy}$	...	...	...	...	...	...
51	7,9-Di-Me-8-oxa–65	3	–O–	*p*-FC_6H_4	...	..	$C_{19}H_{29}ClFNO_2^{zz}$	...	...	...	...	...	...
52	4,4-Di-Me–piperidine	3	–O–	*p*-FC_6H_4	105–110 (0.13)	89	$C_{16}H_{24}FNO^{aaa}$	72.42	9.12	5.28	72.55	9.03	5.36
53	4,4-Di-Et–piperidine	3	–O–	*p*-FC_6H_4	115–120 (0.1)	80	$C_{18}H_{28}FNO^{bbb}$	73.68	9.62	4.77	73.69	9.54	4.85
54	4-Me-4-Pr–piperidine	3	–O–	*p*-FC_6H_4	120–130 (0.22)	86	$C_{18}H_{28}FNO^{ccc}$	73.68	9.62	4.77	73.51	9.49	4.90
55	4-Phenyl-4-carboethoxy–piperidine	3	–O–	*p*-FC_6H_4	175–185 (0.15)	80	$C_{23}H_{23}FNO_3^{ddd}$	71.66	7.32	3.63	71.43	7.53	3.90
56	66	2	...	–OH	140–144 (12)	91	$C_{12}H_{23}NO^{eee}$	73.04	11.75	7.10	72.88	11.61	6.85
57	66	2	...	–Cl	...	98	$C_{12}H_{23}Cl_2N^{fff}$	...	...	...	...	...	...
58	66	3	...	–Cl	...	86	$C_{13}H_{25}Cl_2N^{ggg}$	...	...	...	...	...	...
59	66	3	...	–Cl	94–96 (0.15)	86	$C_{13}H_{24}ClN^{hhh}$	...	...	...	...	...	...
60	66	4	...	–OH	120–125 (0.3)	89	$C_{14}H_{27}NO^{iii}$	74.61	12.08	6.22	74.66	12.18	5.90
61	66	4	...	–Cl	...	85	$C_{14}H_{27}Cl_2N^{jjj}$	...	...	...	...	...	...
62	66	5	...	–OH	130–136 (0.13)	88	$C_{15}H_{29}NO^{kkk}$	75.26	12.21	5.85	74.89	11.91	5.77
63	66	5	...	–Cl	...	85	$C_{15}H_{29}Cl_2N^{lll}$	...	...	...	...	...	...
64	9-Me–66	6	...	–OH	140–150 (0.27)	81	$C_{17}H_{33}NO^{mmm}$	76.34	12.44	5.24	76.28	12.62	5.21
65	9-Me–66	6	...	–Cl	...	90	$C_{17}H_{33}Cl_2N^{nnn}$	...	...	...	...	..	...
66	66	6	...	–CN	135–145 (0.3)	87	$C_{17}H_{30}N^{ooo}$	77.80	11.52	10.68	77.51	11.41	10.46
67	66	7	...	$–NH_2$	135–135 (0.3)	71	$C_{17}H_{34}N_2^{ppp}$	76.63	12.86	10.51	76.54	12.63	10.40
68	55	3	–CO–	*p*-FC_6H_4	133–137 (0.25)	63	$C_{18}H_{21}FNO^{qqq}$	74.71	8.36	4.84	74.73	8.47	4.83

TABLE II (*Footnotes*)

[a] The central chain is reversed placing the –CO– group on the ring nitrogen giving the amide. *Anal.* Calcd.: Br, 22.81. Found: Br, 22.97. [b] Hydrochloride, m.p. 171–172°, from methanol–ether. *Anal.* Calcd. for $C_{19}H_{27}ClFNO$: Cl, 10.43. Found: Cl, 10.27. [c] Fluorine. [d] Hydrochloride, m.p. 159–160° from acetone–ether. *Anal.* Calcd. for $C_{20}H_{29}ClFNO$: Cl, 10.02. Found: Cl, 9.82. [e] Base, m.p. 64–65° from ligroin. Hydrochloride, m.p. 241–242° from methanol–ether. *Anal.* Calcd. for $C_{19}H_{27}ClFNO$: Cl, 10.43. Found: Cl, 10.34. Methiodide, m.p. 225–226° from methanol–ether. *Anal.* Calcd. for $C_{20}H_{29}FINO$: I, 28.50. Found: I, 28.82. [f] Base, m.p. 52–53° from ligroin. Hydrochloride, m.p. 236–237° from acetone. *Anal.* Calcd. for $C_{20}H_{29}ClFNO$: C, 67.87; H, 8.26; F, 5.37. Found: C, 67.86; H, 8.34; F, 5.49. Methiodide, m.p. 226–227° dec. from methanol–ether. *Anal.* Calcd. for $C_{21}H_{31}FINO$: I, 27.63. Found: I, 27.91. [g] From the positional isomer, 1-azaspiro[4.5]decane. Hydrochloride, m.p. 149–151° from acetone–ether. *Anal.* Calcd. for $C_{19}H_{27}ClFNO$: Cl, 10.43. Found: Cl, 10.18. [h] As the hydrochloride, m.p. 223–224° from acetone–ether. [i] As the hydrochloride, m.p. 256–257° from acetone–petroleum ether (b.p. 30–60°) or from water. [j] Hydrochloride, m.p. 244–245° from methanol–ether. *Anal.* Calcd. for $C_{21}H_{31}ClFNO$: Cl, 9.64. Found: Cl, 9.55. Methiodide, m.p. 205–206° from acetone. *Anal.* Calcd. for $C_{22}H_{33}FINO$: I, 26.81. Found: I, 27.06. [k] Base, m.p. 91–92° from acetone–hexane. Partial decomposition on distillation unless carried out rapidly. Hydrochloride, m.p. 271–272° dec. from methanol–ether. *Anal.* Calcd. for $C_{21}H_{37}ClFNO$: Cl, 8.65. Found: Cl, 8.55. Methiodide, m.p. 220–221° from methanol–ether. *Anal.* Calcd. for $C_{25}H_{39}FINO$: I, 24.62. Found: I, 24.60. [l] As hydrochloride, m.p. 221–222° from acetone–ether. *Anal.* Calcd.: Cl, 9.69. Found: Cl, 9.56. [m] Base, m.p. 64–65° from acetone–water. Hydrochloride, m.p. 249–250° from acetone–ether. *Anal.* Calcd. for $C_{21}H_{31}ClFNO$: Cl, 9.64. Found: Cl, 9.92. Methiodide, m.p. 202–204° from acetone. *Anal.* Calcd. for $C_{22}H_{33}FINO$: I, 26.81. Found: I, 26.90. [n] As hydrochloride, m.p. 263–264° from acetone–ether. *Anal.* Calcd.: Cl, 8.13. Found: Cl, 7.98. [o] Analysis for the hydrochloride, m.p. 226–227.5° from methanol–acetone. [p] From 9-methyl-3,9-diazaspiro[5.5]undecane. As dihydrochloride, m.p. 285–287° dec. from ethanol–ether. *Anal.* Calcd.: Cl, 17.51. Found: Cl, 17.56. [q] Lidocaine type, as hydrochloride, m.p. 266–267° from ethanol–ether. [r] Procaine type, as dihydrochloride, m.p. 224–225° from ethanol–ether. The N-substituent on the azaspirane ring is *p*-chlorobenzhydryl. As hydrochloride, m.p. 285–286° from methanol–acetone or methanol–water. [t] Saccharin nucleus, N-substituted, m.p. 128.5–129° from acetone–ligroin. [u] Sulfur. Hydrochloride, m.p. 232–233° from ethanol–ether. *Anal.* Calcd. for $C_{18}H_{28}ClNOS$: Cl, 10.37. Found: Cl, 10.28. Methiodide, m.p. 215–216° from ethanol. *Anal.* Calcd. for $C_{19}H_{30}INOS$: I, 28.37. Found: I, 28.34. [v] Base, m.p. 94.5–95.5° from ligroin. Hydrochloride, m.p. 261–262° from methanol–ether. *Anal.* Calcd. for $C_{21}H_{31}ClFNO$: Cl, 9.64. Found: Cl, 9.52. Methiodide, m.p. 180–181° from methanol–ether. *Anal.* Calcd. for $C_{22}H_{33}FINO$: I, 26.81. Found: I, 26.97. [w] *trans*-Decalin-2,4′-piperidine. [x] As hydrochloride, m.p. 248–249° from acetone–ether. *Anal.* Calcd. for $C_{24}H_{35}ClFNO$: Cl, 8.69. Found: Cl, 8.62. [y] Hydrochloride, m.p. 143–144° from acetone–ether. *Anal.* Calcd. for $C_{20}H_{29}ClFNO_2$: Cl, 9.59. Found: Cl, 9.51. Methiodide, m.p. 128–129° from ethyl acetate. *Anal.* Calcd. for $C_{21}H_{31}FINO_2$: I, 26.70. Found: I, 26.64. [z] Hydrochloride, m.p. 177–178° from ethanol–ether. *Anal.* Calcd. for $C_{18}H_{27}ClFNO$: C, 63.03; H, 7.40; Cl, 12.40; N, 4.90. Found: C, 62.80; H, 7.48; Cl, 12.38; N, 4.85. [aa] Analysis for hydrochloride, m.p. 232–233° from ethanol–ether. *Anal.* Calcd.: Cl, 11.30. Found: Cl, 11.26. [bb] Analysis for hydrochloride, m.p. 224–225° from ethanol–ether. *Anal.* Calcd.: Cl, 10.37. Found: Cl, 10.26. [cc] Analysis for hydrochloride, m.p. 209–210° from ethanol–ether. *Anal.* Calcd.: Cl, 10.37. Found: Cl, 10.45. [dd] Analysis for hydrochloride, m.p. 163–164° from ethanol–ether. *Anal.* Calcd.: Cl, 12.32. Found: Cl, 12.32. [ee] Hydrochloride, m.p. 114–115° from ethyl acetate. *Anal.* Calcd. for $C_{17}H_{25}ClFNO$: Cl, 11.30. Found: Cl, 11.48. [ff] As hydrochloride, m.p. 152–153° from ethyl acetate. *Anal.* Calcd.: Cl, 10.81. Found: Cl, 10.78. [gg] As hydrochloride, m.p. 161–162° from acetone. *Anal.* Calcd.: Cl, 10.81. Found: Cl, 10.83. [hh] As hydrochloride, m.p. 219–220° from acetone. *Anal.* Calcd.: Cl, 10.81. Found: Cl, 10.65. [ii] Hydrochloride, m.p. 218–219° from methanol–ether. *Anal.* Calcd. for $C_{18}H_{27}ClFNO$: C, 65.94; H, 8.30; Cl, 10.81. Found: C, 65.76; H, 8.40; Cl, 10.52. Methiodide, m.p. 152–153° from methanol–ether. *Anal.* Calcd. for $C_{19}H_{29}FINO$: C, 52.66; H, 6.75; I, 29.29. Found: C, 52.35; H, 6.75; I, 29.20. [jj] Hydrochloride, m.p. 237–238° from acetone. *Anal.* Calcd. for $C_{19}H_{29}ClFNO$: Cl, 10.37. Found: Cl, 10.29. [kk] Hydrochloride, m.p. 239–240° from acetone. *Anal.* Calcd. for $C_{19}H_{29}ClFNO$: Cl, 10.37. Found: Cl, 10.47. [ll] Hydrochloride, m.p. 239–240° from acetone. *Anal.* Calcd. for $C_{19}H_{29}ClFNO$: Cl, 10.37. Found: Cl, 10.46. [mm] Hydrochloride, m.p. 224–225° from acetone. *Anal.* Calcd. for $C_{20}H_{29}ClF_3NO$: Cl, 9.05. Found: Cl, 8.81. [nn] As hydrochloride, m.p. 258–259° dec. from acetone–ethyl acetate. *Anal.* Calcd.: Cl, 9.96. Found: Cl, 9.74. [oo] As hydrochloride, m.p. 273–274° from methanol–acetone. *Anal.* Calcd.: Cl, 8.91. Found: Cl, 9.04. [pp] As hydrochloride, m.p. 235–237° from methanol–acetone. *Anal.* Calcd.: Cl, 19.79. Found: Cl, 19.60. [qq] As hydrochloride, m.p. 218–219° from methanol–acetone. *Anal.* Calcd.: Cl, 10.92. Found: Cl, 10.32. [rr] Hydrochloride, m.p. 231–232° from acetone. *Anal.* Calcd. for $C_{19}H_{29}ClFNS$: C, 63.75; H, 8.17; Cl, 9.90. Found: C, 64.08; H, 8.17; Cl, 9.82. [ss] As hydrochloride, m.p. 242–243° from ethanol. *Anal.* Calcd.: Cl, 9.53. Found: Cl, 9.42. [tt] As hydrochloride, m.p. 246–247° from ethanol. *Anal.* Calcd.: Cl, 9.10. Found: Cl, 8.91. [uu] As hydrochloride, m.p. 218–222° from ethanol. *Anal.* Calcd.: Cl, 9.09. Found: Cl, 9.10. [vv] Hydrochloride, m.p. 208–209° from acetone. *Anal.* Calcd. for $C_{20}H_{31}ClFNO$: Cl, 9.96. Found: Cl, 10.09. Methiodide, m.p. 160–161° from acetone. *Anal.* Calcd. for $C_{21}H_{33}FINO$: I, 27.51. Found: I, 27.29. [ww] Hydrochloride, m.p. 234–235° from acetone. *Anal.* Calcd. for $C_{19}H_{33}ClFNO$: Cl, 9.58. Found: Cl, 9.31. [xx] As hydrochloride, m.p. 263–264° from methanol–acetone. *Anal.* Calcd.: Cl, 9.96. Found: Cl, 10.22. Methiodide, m.p. 174–175° from acetone–ethyl acetate. *Anal.* Calcd. for $C_{21}H_{35}FINO$: I, 27.51. Found: I, 27.20. [yy] As hydrochloride, m.p. 264–265° from acetone. *Anal.* Calcd.: Cl, 8.95. Found: Cl, 8.80. [zz] As hydrochloride, m.p. 139–140° from ethyl acetate. *Anal.* Calcd.: Cl, 9.91. Found: Cl, 9.94. [aaa] Hydrochloride, m.p. 215–216° from acetone. *Anal.* Calcd. for $C_{19}H_{29}ClFNO$: Cl, 11.75. Found: Cl, 11.49. Methiodide, m.p. 204–205° from methyl ethyl ketone. *Anal.* Calcd. for $C_{15}H_{27}FINO$: I, 31.16. Found: I, 31.43. [bbb] Hydrochloride, m.p. 210–211° from acetone. *Anal.* Calcd. for $C_{18}H_{29}ClFNO$: Cl, 10.75. Found: Cl, 10.71. Methiodide, m.p. 156–157° from acetone. *Anal.* Calcd. for $C_{19}H_{31}FINO$: I, 29.15. Found: I, 29.41. [ccc] Hydrochloride, m.p. 234–235° from methanol–acetone. *Anal.* Calcd. for $C_{18}H_{29}ClFNO$: Cl, 10.75. Found: Cl, 10.83. Methiodide, m.p. 142–143° from acetone. *Anal.* Calcd. for $C_{19}H_{31}FINO$: I, 29.15. Found: I, 28.88. [ddd] Hydrochloride, m.p. 198.5–199° from acetone. *Anal.* Calcd. for $C_{20}H_{29}ClFNO_3$: Cl, 8.40. Found: Cl, 8.21 [eee] Hydrochloride, m.p. 178–180° from acetone–ether. *Anal.* Calcd. for $C_{19}H_{27}ClNO$: Cl, 15.17. Found: Cl, 15.01. [fff] As hydrochloride, m.p. 267.5–268° from methanol–acetone. *Anal.* Calcd.: Cl, 28.11. Found: Cl, 27.93. [ggg] Hydrochloride, m.p. 259–260° from methanol–ether. *Anal.* Calcd.: Cl, 26.63. Found: Cl, 26.43. [hhh] *Anal.* Calcd.: Cl, 15.43. Found: Cl, 15.27. Methiodide, m.p. 206–207° from acetone. *Anal.* Calcd. for $C_{17}H_{27}ClIN$: I, 34.14. Found: I, 33.98. [iii] Hydrochloride, m.p. 157–158° from methylene chloride–ether. *Anal.* Calcd. for $C_{14}H_{28}ClNO$: Cl, 13.54. Found: Cl, 13.45. Methiodide, m.p. 157–158° from acetone. *Anal.* Calcd. for $C_{15}H_{30}INO$: I, 34.56. Found: I, 34.53. [jjj] As hydrochloride, m.p. 203–204° from methanol–ether. *Anal.* Calcd.: Cl, 25.30. Found: Cl, 25.12. [kkk] Hydrochloride, m.p. 187.5–188.5° from methylene chloride–ether. *Anal.* Calcd. for $C_{15}H_{30}ClNO$: Cl, 12.85. Found: Cl, 12.70. [lll] Hydrochloride, m.p. 249–250° from acetone. *Anal.* Calcd.: Cl, 24.09. Found: Cl, 24.05. [mmm] Hydrochloride, m.p. 163–164° from acetone. *Anal.* Calcd. for $C_{17}H_{31}ClNO$: Cl, 11.67. Found: Cl, 11.43. Methiodide, m.p. 183–184° from acetone. *Anal.* Calcd. for $C_{18}H_{36}INO$: I, 31.00. Found: I, 30.76. [nnn] As hydrochloride, m.p. 281–282° dec. from acetone. *Anal.* Calcd.: Cl, 22.00. Found: Cl, 21.89. [ooo] Hydrochloride, m.p. 232–233° from acetone–ether. *Anal.* Calcd. for $C_{17}H_{31}ClN_2$: Cl, 11.86. Found: Cl, 11.75. Methiodide, m.p. 120–121° from acetone. *Anal.* Calcd. for $C_{18}H_{33}IN_2$: I, 31.38. Found: I, 31.46. [ppp] Dihydrochloride, m.p. 270–272° from methanol–ether. *Anal.* Calcd. for $C_{17}H_{30}Cl_2N_2$: Cl, 20.89. Found: Cl, 20.78. [qqq] Hydrochloride, m.p. 147–148° from acetone–ether. *Anal.* Calcd. for $C_{18}H_{29}ClFNO$: Cl, 10.88. Found: Cl, 10.82.

TABLE III

SUMMARY OF PHARMACOLOGICAL OBSERVATIONS[a]

Compd.[b]	LD_{50}/72 hr.[c]	ED[d]	Dec. motor activity	Ataxia	Anti-morphine	Anti-tremorine	DES[e]	Anti-inflam-matory	Sedation	Hypo-tension	Anal-gesia[f]	Remarks[g]
CPZ[h]	...	...	12.7	12.7	6.6	1.4	+	...	++++	+	2/6	T, H
HP[i]	...	...	4.0	...	0.8	~0.6	+	...	...	+	2/6	T, H
1	>200	...	...	...	...	...	..	...	...	...	...	NRR
3	50	<2	12.7	12.7	3.4	5.4	+	...	+++	<0.5	...	T, H
4	50	<2	4.0	...	6.2	4.4	+	...	++	<0.5	...	T, H
5	50	<1	4.0	...	3.2	4.2	+	...	++++	<1.0	2/6	T, H
5·MeI	60	>10	127	...	40	...	+	8	...	...	0/6	NRR
6	50	<1	4.0	4.0	...	...	..	...	+++	<1.0	...	T, H
7	75	>10	127	127	Syn.	7.5	..	...	...	...	...	Little effect at high dose
9	...[j]	<1	3.1	50	3.5	...	+	100	++++	<0.5	2/6	T, H, A
10	50	<1	12.7	...	13.0	6.6	+	91	++++	<1.0	...	T, H, A
11	60	<1	1.27	127	...	...	+	...	+++	<1.0	...	T, H, A
13	75	<1	4.0	40	2.0	16	+	33	++++	<1.0	2/6	T, H, A
16	100	>10	127	>127	...	...	...	...	...	...	...	NRR
21	30	>10	...	...	...	...	..	10	...	...	...	Convulsant
22	75	<1	12.7	40	3.7	5.0	+	...	+++	<2	...	T, H
23	60	<2	12.7	40	2.2	...	+	...	++	~5	...	T, H
24	75	<2	12.7	12.7	...	...	..	...	++	<5	...	T, H
34	50	<3	...	...	...	...	..	...	...	...	...	Convulsant
37	75	<5	...	...	...	...	..	...	+	<5	...	T, H, mild
38	150	<10	...	...	...	...	..	...	+	>10	...	T, H, mild
68	60	<1	4.0	...	3.9	4.4	+	...	++	<5	...	T, H

[a] Values are given in mg./kg. to produce effect noted. Dots, . . . , under the respective headings do not mean no effect, but rather that values were not ascertained under comparable conditions for all the compounds. Sedation is rated: +, mild or slight; ++, moderate; +++, marked; ++++, very marked. [b] Numbers for the compounds in this table refer to the numbers in Table II. [c] Approximate LD_{50}/72 hr. determined on i.p. administration to Wistar rats. [d] Although the various parameters for which values are presented in the table were of necessity not all determined in the same species, the effective dose to produce noticeable effect, most frequently tranquilization, was that given which produced this effect in most or all of the species used, *i.e.*, mouse, rat, cat, dog, and Rhesus monkey. [e] Decrease in electroshock threshold: + indicates a decrease was observed. [f] In the rat at 25 mg./kg. *p.o.* [g] Abbreviations used: T, tranquilization; H, hypotension; A, antiinflammatory; NRR, no remarkable reaction. [h] Chlorpromazine. [i] Haloperidol. [j] Acute LD_{50}, mg./kg.: in the rat, *p.o.* 200, i.p. 60; in the mouse, *p.o.* 120, i.p. 45.

parent that structural features necessary for optimal tranquilizing activity are: (a) Q = –CO–, (b) n = 3, and (c) R–C = *p*-fluorophenyl. The optimal size and configuration of the basic azaspiranyl moiety is not readily ascertainable as there were many compounds in which these permutations were made (**2**–**6**, **9**–**11**, **13**, **14**, **22**–**24**, and **68**) which had the same order of potency in a number of the screens. Substituents, other than fluorine, on ring C (**8**, **12**, **41**, and **42**), although active, were much less potent. Reduction of the carbonyl Q group (**15**) or the substitution of –O– or –S– for –CO– (**30**–**34**, **37**, **38**, **40**, and **43**) resulted in decreased potency. However, the derivatives in which Q was –O– and R–C was *p*-fluorophenyl were moderately potent tranquilizers. There was no remarkable difference between compounds in which Q was ether or thioether (**37** and **43**).

Oxidation of the thioether group to the sulfone resulted in almost complete loss of CNS depressant properties (**44**–**46**). These compounds were devoid of tranquilizing and antiinflammatory activity, produced slight hypotension; compound **46**, with the *p*-fluorophenyl substituent, had mild antitremorine activity.

Compounds **35**–**38** represent a study of the effect of the position of the fluorine substituent on ring C. Although the *para* position seems to confer greatest potency, the differences were not great. Separation of the fluorine atom from the aromatic ring, although not strictly comparable, as in **38**, resulted in decreased potency. Compounds **34**, **37**, **47**, and **48** were studied for effects of variation of n. Activity was optimal when n = 3.

Other permutations which decreased or abolished CNS depressant activity were (a) decreased basicity of the azaspiranyl moiety as in the amide **1** [the nonbasic nitrogen atom in the saccharin nucleus (**20**) also gave an inactive compound when other structural features were optimal for activity]; (b) introduction of another basic center into ring A of the azaspiranyl moiety as in **16**; (c) quaternization of the azaspiranyl ring B nitrogen as in **5**·MeI; and (d) changing the position of the nitrogen atom in ring B to the 1-position adjacent to the spiro carbon atom.

Modifications (a)–(c) produce rather drastic changes in the basic nature of the azaspiranyl ring B nitrogen. The most remarkable change in activity was that observed with the 1-positional isomer (**7**) of compound **3** since this modification would be expected to produce the least effect on the over-all structural requirements for optimal activity. While compound **3** was a potent CNS depressant, its 1-positional isomer (**7**) was devoid of tranquilizing properties and resulted in a separation of antimorphine and antitremorine effects.

Compound **24**, with an additional hetero oxygen atom in ring A, was quite potent as a CNS depressant, but of quicker onset and shorter duration of action than the carbocyclic ring A compounds with identical N-substituents.

Opening of the A ring to give 4,4-disubstituted piperidines (**25**–**28**) yielded compounds which were less potent CNS depressants than the azaspiranyl Y–AB structure. Doses of 5–10 mg./kg. (which produced marked effect in the closed A-ring group) had little effect on the behavior of cats. However, they retained many of the properties of the closed A-ring structures, *i.e.*, antimorphine, antitremorine, and 0.25–0.33 the antiinflammatory activity of **9**. The piperidine ring (**25**) was about equal in potency to the 4,4-dialkyl substituted piperidines with the exception of decreased antitremorine activity. The 4,4-dimethylpiperidine structure was most potent of this type in that respect, but at higher doses augmented the other tremorine autonomic effects. The morpholine derivative (**29**) had no outstanding properties. Replacement of the –CO–, Q group, by –O– (**52**–**55**) lessened potency as was the case with the closed A-ring structures.

Compound **21**, in which phenyl was replaced by thienyl in the side chain, had little effect on the behavior of cats or mice up to near toxic doses. It did show some limbic system differential excitability in cats at convulsive doses and had weak antiinflammatory activity.

The two compounds, **17** and **18**, in which the 66-azaspiranyl ring system was substituted for the amine portion of lidocaine and procaine, showed no remarkable local anesthetic activity.

Based upon the screening data, which did not permit the selection of the optimal azaspiranyl moiety, compound **9**[11] was selected for more detailed investigation since it was among the more potent compounds, had a wide spectrum of activity in the screens, and starting materials for its preparation on a large scale were more readily accessible than those for some of the other potent members of the group. It was compared directly with chlorpromazine (CPZ) and haloperidol (HP) in these evaluations. It is interesting to note that this compound was found to have identical i.p. toxicity in mice with that reported for HP.[11]

In mice spontaneous motor activity was depressed approximately the same on short-term experiments (1 hr.) by CPZ 5.0 mg./kg., HP 1.0 mg./kg., and **9** 2.5 mg./kg. Compound **9** had the most rapid onset of action by both *p.o.* and i.p. routes. On the longer term experiments (up to 16 hr.) **9** had the shortest duration of action of the three drugs.

A comparison of the suppression of spontaneous and forced motor activity showed that **9** and HP suppressed spontaneous more than forced motor activity. It has been the frequently expressed opinion that tranquilizers should suppress spontaneous more than forced motor activity. Compound **9** had a sharp dose–response relationship on *p.o.* administration during these studies of effect on motor activity.

In the conditioned avoidance and approach behavior studies the order of potency was HP > **9** > CPZ. HP and **9** caused a large increase in shock taken by the animals while CPZ was much less effective. At 2.5 mg./kg. i.p. the average inhibitions of food consumption and running to obtain food were HP, 95%; **9**, 85%; and CPZ, 65%.

During studies of the potentiation of electroshock convulsant activity it became apparent that there were differences between HP, CPZ, and **9**. At doses of 1–10 mg./kg. CPZ and HP potentiated convulsant activity of the electroshock. Up to 5 mg./kg. these effects were most marked. With CPZ and HP, 50–67% of the animals convulsed, while with **9** less than 20% convulsed. At doses >10 mg./kg. the situation was reversed. HP and CPZ suppressed convulsant activity at 25–50 mg./kg. while **9** potentiated it.

The observations on electroshock–drug effects carried over into the EEG studies in cats. At doses <10 mg./kg., **9** produced effects similar to those seen with phenothiazine tranquilizers. At doses >10 mg./kg., convulsant activity was noted, and at intermediate doses (10–20 mg./kg.) there was observed in some cases differential convulsive seizure in the limbic areas. At higher doses (20–30 mg./kg.) generalized EEG convulsive activity, accompanied by marked autonomic effects, clonic and tonic motor convulsions, resulted. Convulsive activity produced by intermediate doses could frequently be prevented or controlled by pentobarbital, 3–5 mg./kg. i.p. or i.v.

In cats, **9** at 5–10 mg./kg. produced behavioral and reflex effects similar to those seen with the same doses of CPZ. In Rhesus monkeys, the effects of **9** were most marked. At 0.15–0.30 mg./kg. slight to moderate sedation, without ataxia or ptosis, was observed up to 24 hr. At 0.5–1.0 mg./kg., marked sedation, catelepsy, slight ataxia, and loss of muscle tone were seen up to 48 hr. At 2.0 mg./kg., the animals exhibited marked depression, ataxia, ptosis, blanched faces, reacted slowly and weakly to stimuli, and would not eat. Appetite had been unaffected up to 1.25 mg./kg. With **9** these effects persisted, with attenuation, up to 3 days, while with CPZ at equal doses there was little effect and no carryover. HP effects seemed to persist as long or longer than those of **9**. This was in marked contrast with the findings with smaller animals wherein **9** seemed to have a shorter duration of action than CPZ.

In anesthetized and unanesthetized cats (1 mg./kg. or more) and dogs (0.1 mg./kg. or more) **9** lowered both systolic and diastolic blood pressure significantly for more than 60 min.; and in dogs a dose–response relationship was evident in the range 0.1–11.0 mg./kg. Doses of 0.1, 1.0, and 10.0 mg./kg. either i.a. or i.v. in dogs gave 17, 40, and 45% average lowering of systolic and diastolic blood pressure accompanied by bradycardia (10–12%) and increased myocardial contractile force (3–7%). Higher or cumulative doses produced rather inconsistent responses of heart rate and contractile force.

Hind leg perfusion studies in dogs showed that i.a. or i.v. administration of **9** decreased vascular resistance (10 mg. of **9** was approximately equivalent to 1 γ of acetyl choline) and reduced or reversed the pressor effects of epinephrine and norepinephrine. Compound **9** had weak antiserotonin and antihistamine activity. The concentrations required to decrease the contractions of the isolated guinea pig ileum by 50%, produced by serotonin and histamine, were 10 and 8 mg./l., respectively. The very potent hypotensive activity of *p*-fluoroaroylalkyl azaspiranes can thus be attributed in part to their production of a decrease in vascular resistance and blocking of epinephrine, norepinephrine, and weak antiserotonin effects.

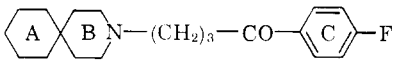
(11) Under study by Wyeth Laboratories, Inc. under code Wy-3457.

Clinical.—Several of the *p*-fluoroaroylalkylazaspiranes were found to possess potent CNS depressant, hypotensive, and antiinflammatory activity, and to be clinically effective tranquilizers (**2, 5, 6, 9–11, 13, 22,** and **68**) at doses of 5 to 10 mg., b.i.d. or t.i.d.[15]

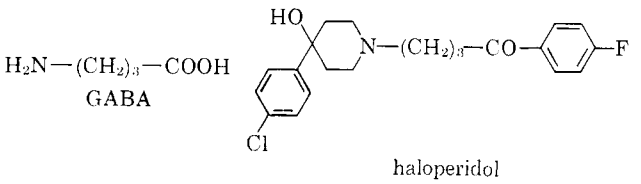
Based upon the pharmacological findings, particularly the differential limbic system activation observed in EEG studies in cats and the fact that drug (pentylenetetrazol) and electroshock-induced convulsive activity have long been used in the treatment of schizophrenics, **9** was tested clinically in a mental institution.[16,17] The subjects were 30 male chronic schizophrenics, age 20–57 years (av. 46.7 years), with 2–24 years (av. 22.1 years) hospitalization who were resistant to other therapy.

Compound **9** had marked antipsychotic effect at low dosage. Behavioral and toxicity effects were similar to those of HP. Treatment was continued for periods up to 20 weeks and doses were pushed as high as 300 mg./day, or 10 times the maximum recommended dose. In 9 of 30 patients improvement was noted during therapy and one patient showed marked and 2 moderate improvement. At the high doses employed in these trials a stimulant effect was noted in 8 of the 30 patients.

Toxicity effects noted at these high doses were on the skin and hair, consisting of folliculitis, ichthyosis, and hair loss, and were reversible on discontinuance of therapy. Two Puerto Rican and three Negro patients did not manifest the toxic symptoms seen in whites. Since many of the toxic symptoms resembled those seen with triparanol, a study of the blood cholesterol levels showed that **9** lowered blood cholesterol apparently by blocking synthesis in the post squalene stage.[17]



9



haloperidol

It was thought that the drug might be of beneficial effect to hebephrenic schizophrenics. However, its action on catatonic schizophrenics was most marked.

Structure–Activity Relationships. Y-ABN-$(CH_2)_n$-Q-C-R.—The most active compounds of this group were those in which Q was –CO–, C–R was an aryl group, particularly *p*-fluorophenyl, Y–AB was an azaspiranyl moiety, and *n* was 3. This was also the case with Janssen's compounds when the B ring was piperidine and A contained another ring substituted on the piperidine ring. In our series there was a clearcut decrease in activity when *n* was 2 or 4 (**34** and **47**). Opening of the B ring also led to decreased activity.[18]

The similarity of the central chain bearing the C–R and Y–AB substituents to γ-aminobutyric acid (GABA) is striking. The CNS pharmacology of GABA has been the subject of numerous reviews.[19] Purpura, *et al.*,[20] showed by electrophysiological measurements that only ω-amino acids were synaptically active inhibitors, that α-amino acids and α,ω-diamino acids were not inhibitors, that activity decreased with increasing or decreasing chain length from GABA, and that glycine, the simplest ω-amino acid, retained some activity.

The CNS depressant properties of butyrate, 4-hydroxybutyrate,[21] and butyrolactone[22–25] have been reported. The lactone was the most potent, had the quickest onset of action of the group, and produced hypnosis, muscle relaxation without analgesia or notable respiratory depression in animals and clinically.

γ-Valerolactone was inactive while propiolactone has been reported to be a carcinogen.[26] It thus appears that of these structures a structural and a spatial charge distribution relationship to GABA is essential for activity.

Experimental

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

2-Azaspiro[4.4]nonane-1,3-dione.—Cyclopentane-1-carboxy-1-acetic acid anhydride (15.4 g., 0.1 mole) was allowed to react with excess concentrated aqueous ammonia, heated slowly to 180°, and cyclized at 180° for 0.5 hr. to give the product quantitatively, m.p. 115–118°. After two recrystallizations from acetone–water, it melted at 120–122°.

2-Azaspiro[4.4]nonane.—The preceding imide (13 g., 0.084 mole), dissolved in 300 ml. of anhydrous absolute ether, was added with stirring to a solution of 8 g. of lithium aluminum hydride in 500 ml. of ether. The mixture was stirred 4 hr., decomposed by slow dropwise addition of water, filtered free of inorganic materials, and dried (Na_2SO_4) overnight, the ether was stripped off, and the amine was distilled under reduced pressure to give 8.5 g. (81%), b.p. 70° (14 mm.).

The **picrate** was obtained by adding 0.1 ml. of the amine to 10 ml. of a saturated solution of picric acid in methanol. It crystallized in diamond-shaped prisms, m.p. 161.5–162°. The **hydrochloride,** obtained by bubbling gaseous HCl through an ether solution of the base, was extremely hygroscopic and impractical to handle. The **hydrobromide,** obtained as a by-product from the synthesis of **30,** was not hygroscopic and melted at 92–95° and at 99–100° after two recrystallizations from ethyl acetate.

3-Azaspiro[5.5]undecane-2,4-dione.—This imide was obtained quantitatively by reaction of cyclohexane-1,1-diacetic anhydride with concentrated aqueous ammonia followed by cyclization at 180° for 1 hr. It melted at 168–169° on recrystallization from ethanol, water, or acetone–water.

(15) C. F. Geschickter, personal communication.

(16) G. M. Simpson, T. Farkas, and J. C. Saunders, *Psychopharmacologia*, **5**, 306 (1964).

(17) G. M. Simpson, J. H. Blair, and E. H. Cranswick, *Clin. Pharm. Therap.*, **5**, 310 (1964).

(18) In this connection W. J. Humplett, M. J. Weiss, and C. R. Hauser [*J. Am. Chem. Soc.*, **70**, 4020 (1948)] made a group of butyrophenones in which AB was diethyl (equivalent to removal of ring A and opening of ring B) which were used as intermediates for the synthesis of quinacrine analogs and which were screened for antimalarial and antitubercular activity. As no CNS properties were reported, it would be interesting to compare the effects of this structural change with our results.

(19) "Inhibition in the Nervous System and Gamma-Aminobutyric Acid," Proceedings of the International Symposium, Duarte, Calif., May 1959, Pergamon Press (1960).

(20) D. P. Purpura, M. Girado, and H. Grundfest, *Proc. Soc. Exptl. Biol. Med.*, **95**, 791 (1957).

(21) J. Jouany, J. Gérard, and H. Laborit, *Compt. rend. soc. biol.*, **154**, 1206 (1960).

(22) J. Jouany, J. Gérard, H. Laborit, and P. Carlo, *ibid.*, **154**, 2039 (1960).

(23) M. Jouvet, A. Cier, D. Mounier, and J. L. Valatx, *ibid.*, **155**, 1313 (1961).

(24) P. Benda and R. Perles, *Compt. rend.*, **251**, 1312 (1960).

(25) N. J Giarman and K. F. Schmidt, *Brit. J. Pharmacol.*, **20**, 563 (1963).

(26) F. Dickens and H. E. H. Jones in "British Empire Cancer Campaign," 1961, p. 7.

3-Azaspiro[5.5]undecane.—Reduction of 60 g. (0.33 mole) of the preceding imide with 24 g. of lithium aluminum hydride in ether gave 36 g. (71%) of the azaspirane base with b.p. 110–112° (20 mm.) or 114° (23 mm). Several preparations of this material gave 70–75% yields when the imide was added as a slurry in ether. By adding the imide dissolved in benzene, or by extraction overnight with ether in a Soxhlet apparatus into the lithium aluminum hydride solution in ether, yields up to 85% were realized.

The **picrate,** prepared in methanol–saturated picric acid, melted at 193–194°. The **hydrochloride,** prepared in ether with alcoholic HCl, melted at 239–240°. The **hydrobromide,** obtained from the preparation of **35,** melted at 200–201° on recrystallization from acetone.

3-(3-Benzoylpropyl)-3-azaspiro[5.5]undecane Hydrochloride.—3-Azaspiro[5.5]undecane (15.3 g., 0.1 mole), 9.1 g. (0.05 mole) of 4-chlorobutyrophenone, and 0.1 g. of KI were refluxed in 100 ml. of toluene for 2 days. On cooling, 250 ml. of ether was added, **3-azaspiro[5.5]undecane hydrochloride** was removed by filtration, all solvents were stripped, the residue was dissolved in ether, filtered, and treated with gaseous HCl to give the product (9.8 g., 58%). It melted at 218–221° and at 223–224° on recrystallization from acetone–ether or water.

8-Methyl-3-[3-(*p*-fluorobenzoyl)propyl]-3-azaspiro[5.5]undecane was prepared as the preceding compound (0.05 *M* scale) except that, after drying and stripping solvents, the base was distilled *in vacuo* to give 14.5 g. (87%), b.p. 150–160° (0.2 mm.).

The **hydrochloride,** obtained by saturating an ether solution of the base with HCl gas, melted at 242–244° and at 244–245° on recrystallization from methanol–ether. The **methiodide,** obtained by refluxing the base in ethyl acetate with an excess of methyl iodide and adding ether, melted at 205–206° on recrystallization from acetone–ether.

3-(*p*-Chlorobenzhydryl)-3-azaspiro[5.5]undecane Hydrochloride.—*p*-Chlorobenzhydryl chloride (10 g., 0.042 mole) in 100 ml. of toluene was added dropwise to a stirred refluxing suspension of 7.5 g. of anhydrous sodium carbonate and 7.5 g. (0.049 mole) of 3-azaspiro[5.5]undecane in 50 ml. of toluene and refluxed 48 hr. The cooled reaction mixture was washed with water and the toluene solution was extracted three times with 10% aqueous HCl. The extracts were filtered and cooled in the freezer to give 11 g. (67%) of the product, m.p. 279–281°. The product melted at 285–286° on recrystallization from methanol–acetone or methanol–water.

2-[4-(*p*-Bromophenyl)butyroyl]-2-azaspiro[4.4]nonane.—2-Azaspiro[4.4]nonane (4 g., 0.032 mole) and 3.3 g. (0.032 mole) of triethylamine were dissolved in 100 ml. of ether and cooled to 10–15°. A solution of 8.4 g. (0.032 mole) of 4-(*p*-bromophenyl)-butyroyl chloride in 50 ml. of ether was added dropwise with stirring. The mixture was stirred for 20 min. and 200 ml. of 30–60° petroleum ether was added. Triethylamine hydrochloride was filtered off, the solvents were stripped, and the product was distilled *in vacuo* to give 9.8 g. (87%), b.p. 170–180° (0.15 mm.).

2-[3-(*p*-Fluorobenzoyl)propyl]-1,2-benzisothiazol-3(2H)-one 1,1-Dioxide.—Saccharin sodium (10.2 g., 0.05 mole) and 4-chloro-4′-fluorobutyrophenone (10 g., 0.05 mole) were refluxed for 24 hr. in 75 ml. of dimethylformamide. The dimethylformamide was removed at the water pump and 200 ml. of water was added. A quantitative yield of crude product, m.p. 123–129°, was obtained. On two recrystallizations from acetone–petroleum ether, it melted at 128.5–129°.

3-[3-(2-Thenoyl)propyl]-3-azaspiro[5.5]undecane.—Freshly distilled 4-chloro-2-butyrothienone[27] (10 g., 0.053 mole) and 16.3 g. (0.106 mole) of 3-azaspiro[5.5]undecane were refluxed overnight in 100 ml. of toluene containing 0.1 g. of KI. The mixture was cooled, diluted with three volumes of ether, and 3-azaspiro-[5.5]undecane hydrochloride was filtered off. All solvents were stripped, and the residue was distilled *in vacuo* to give 14 g. (86%) of product, b.p. 160–170° (0.2 mm.).

The **hydrochloride,** prepared from the base in ether with gaseous HCl, melted at 232–233° on recrystallization from ethanol–ether. The **methiodide,** obtained by refluxing the base in ethyl acetate and adding two volumes of ether, melted at 215–216° on recrystallization from ethanol.

2-(3-Azaspiro[5.5]undecan-3-yl)-2′,6′-acetoxylidide Dihydrochloride ("**Spirolidocaine**").—A solution of 37.2 g. (0.33 mole) of chloroacetyl chloride was added dropwise with stirring to a solution of 36 g. (0.3 mole) of *o,o′*-xylidene in 400 ml. of glacial HOAc at 15°. After stirring 10 min., a solution of 100 g. of NaOAc in 400 ml. of water was added. After cooling to approximately 5°, the crude **N-chloroacetyl-*o,o′*-xylidene** was filtered, washed with water, and recrystallized from alcohol to yield 53.4 g. (90%), melting at 146–148°.

N-Chloroacetyl-*o,o′*-xylidene (10 g., 0.05 mole) and 15.3 g. (0.1 mole) of 3-azaspiro[5.5]undecane were refluxed in 100 ml. of toluene for 4 hr., cooled, and diluted with three volumes of ether. After removal of the precipitated 3-azaspiro[5.5]undecane hydrochloride, the filtrate was washed with water and extracted with 2 l. of 5% HCl. The extract was neutralized with aqueous ammonia, extracted three times with ether, the ether extracts were dried (Na_2SO_4), filtered, and treated with an excess of alcoholic HCl. There was obtained 10.5 g. (60%) of product which melted at 266–267° after recrystallization from alcohol–ether.

2-(3-Azaspiro[5.5]undecan-3-yl)ethanol.—3-Azaspiro[5.5]undecane (58 g., 0.38 mole) was mixed with 50 ml. of absolute methanol and cooled in an ice–calcium chloride freezing mixture. Ethylene oxide was passed in until approximately 20 g. had been absorbed. After standing overnight, the solvents were stripped and the residue was distilled to give 68.5 g. (91%) of product, b.p. 140–144° (12 mm.).

The **hydrochloride,** obtained by treating the base in ether with gaseous HCl, melted at 178–180° after recrystallization from acetone–ether.

2-(3-Azaspiro[5.5]undecan-3-yl)ethanol *p*-Aminobenzoate Dihydrochloride ("**Spiroprocaine**").—2-(3-Azaspiro[5.5]undecan-3-yl)ethanol (9.9 g., 0.05 mole) and 9.3 g. (0.05 mole) of *p*-nitrobenzoyl chloride were refluxed 3 hr. in 100 ml. of toluene and cooled, and two volumes of ether was added. The precipitated crude **2-(3-azaspiro[5.5]undecan-3-yl)ethanol *p*-nitrobenzoate** (17 g., 98%) was not further characterized. The *p*-nitrobenzoate (10 g., 0.029 mole) was dissolved in 200 ml. of ethanol and 50 ml. of methanol, 1 g. of 10% palladium on charcoal was added and hydrogenated in the Parr low-pressure hydrogenator. The catalyst was filtered, the solvents were stripped off, and 10 ml. of alcoholic HCl and 200 ml. of ether were added. The **dihydrochloride** (6 g., 55%) was obtained which melted at 224–226° and at 224–225° on recrystallization from alcohol–ether.

2-(3-Azaspiro[5.5]undecan-3-yl)ethyl Chloride Hydrochloride.—2-(3-Azaspiro[5.5]undecan-3-yl)ethanol (14.8 g., 0.075 mole) in 100 ml. of anhydrous methylene chloride was added dropwise with stirring to 25 g. (0.21 mole) of thionyl chloride in 50 ml. of anhydrous methylene chloride and refluxed 3 hr. On cooling it was diluted with two volumes of ethyl acetate and the product was filtered off and washed with ether. The yield was 17.5 g. On diluting with an equal volume of ether an additional 1 g. of less pure material was obtained to give a total yield of 98%. The product melted at 267.5–268° on recrystallization from methanol–acetone.

3-(3-Azaspiro[5.5]undecan-3-yl)propyl Chloride Hydrochloride.—This was obtained in 86% yield on a 0.14 *M* scale in the same way as the ethyl homolog and melted at 259–260° on recrystallization from methanol–ether.

3-(3-Azaspiro[5.5]undecan-3-yl)propyl Chloride.—The preceding chloride hydrochloride was dissolved in the minimum of water and treated at 10–20° with a slight excess of 10% NaOH and immediately extracted with ether. The extract was dried over Na_2SO_4, the ether was stripped, and the azaspiroalkyl halide was obtained in 93% yield, b.p. 94–96° (0.15 mm.).

The **methiodide,** obtained by refluxing the base with excess methyl iodide in ethyl acetate, cooling, and diluting with two volumes of ether, melted at 206–207°.

3-[3-(*m*-Trifluoromethylphenoxy)propyl]-3-azaspiro[5.5]undecane.—3-(3-Azaspiro[5.5]undecan-3-yl)propyl chloride (5.7 g., 0.025 mole) in 25 ml. of alcohol was added to a solution of 4.1 g. (0.025 mole) of *m*-trifluoromethylphenol and 1.2 g. of NaOH in 25–35 ml. of alcohol, refluxed 4 hr., cooled, and filtered from NaCl. The alcohol was distilled, the residue was dissolved in ether and filtered, the ether was stripped, and the product was obtained on distillation (7 g., 79%), b.p. 130–140° (0.2 mm.).

The **hydrochloride** was obtained by treating the base in ether solution with HCl gas and melted at 224–225° on recrystallization from acetone.

3-(*p*-Fluorophenoxy)propyl Bromide.—*p*-Fluorophenol (56 g., 0.5 mole), 3-chloro-1-propanol (48 g., 0.5 mole), and 21 g. (0.53

(27) The commercial product is very dark. The freshly distilled material, b.p. 85–87° (0.15 mm.), is colorless but begins to turn green in the refrigerator in a few days.

mole) of NaOH were refluxed in 500 ml. of ethanol for 24 hr. The mixture was cooled, NaCl was filtered off, and the alcohol was distilled to yield crude **3-(*p*-fluorophenoxy)-1-propanol.** This material was not further characterized but was esterified directly by refluxing for 24 hr. with a mixture of 120 ml. of 48% aqueous HBr and 20 ml. of concentrated H_2SO_4. The esterification mixture was poured into 2 l. of cold water and extracted twice with 250-ml. portions of ether. The ether extract was dried over Na_2SO_4 overnight and filtered, the ether was stripped off, and the residue was distilled to give 105 g. (90%) of the title compound, b.p. 134–136° (17 mm.). Analytical figures pertain to the entire sample and not a midcut.

Anal. Calcd. for $C_9H_{10}BrFO$: C, 46.38; H, 4.32; Br, 34.28. Found: C, 45.90; H, 4.81; Br, 33.81.

2-[(3-*p*-Fluorophenoxy)propyl]-2-azaspiro[4.4]nonane.—2-Azaspiro[4.4]nonane (5 g., 0.04 mole) and 4.7 g. (0.02 mole) of 3-(*p*-fluorophenoxy)propyl bromide were refluxed for 8 hr. in 30 ml. of toluene. The cooled reaction mixture was diluted with several volumes of ether and precipitated **2-azaspiro[4.4]-nonane hydrobromide** was removed by filtration. The solvents were stripped, and the residue was distilled to give 4.1 g. (75%) of the title compound, b.p. 115–120° (0.24 mm.).

The **hydrochloride,** formed in ether with gaseous HCl, melted at 114–115° after two recrystallizations from ethyl acetate.

5-(3-Azaspiro[5.5]undecan-3-yl)-1-pentanol.—Cyclohexane-1,1-diacetic anhydride (15.5 g., 0.085 mole) and 10 g. (0.085 mole) of 5-aminovaleric acid were dissolved in the minimum of boiling ethyl methyl ketone. The solvent was evaporated and the residue was heated at 180° for 2 hr. to give the corresponding imide, **3-(4-carboxybutyl)-3-azaspiro[5.5]undecane-2,4-dione,** quantitatively. This material was not further characterized but was extracted overnight into a solution of 20 g. of lithium aluminum hydride in 2 l. of absolute ether. The addition complex was decomposed by slow dropwise addition of water and stirred 4 hr. Inorganic salts were filtered off and the inorganic cake was extracted twice with boiling methylene chloride. The ether and methylene chloride extracts were combined and dried overnight over anhydrous sodium sulfate. The solvents were stripped off and the residue was distilled to give the title compound (18 g., 88%), b.p. 130–136° (0.13 mm.).

The **hydrochloride** was formed by treating an ether solution of the amino alcohol with gaseous HCl and melted at 187.5–188.5° after two recrystallizations from methylene chloride–ether.

6-(3-Azaspiro[5.5]undecan-3-yl)hexyl Cyanide.—6-Bromohexyl cyanide (19 g., 0.1 mole) and 30.6 g. (0.2 mole) of 3-azaspiro[5.5]undecane were refluxed for 8 hr. in 150 ml. of toluene containing 0.1 g. of KI. Most of the toluene was distilled at the water pump and 300 ml. of ether was added. Precipitated **3-azaspiro[5.5]undecane hydrobromide** was filtered off, the solvents were stripped, and the residue was distilled to give 22.7 g. (87%) of the title compound, b.p. 135–145° (0.3 mm.).

The **hydrochloride** was obtained on treating an ether solution of the aminonitrile with gaseous HCl and melted at 232–233° on recrystallization from acetone–ether. The **methiodide** was obtained by refluxing the aminonitrile with an excess of methyl iodide for 0.5 hr. in acetone and diluting with several volumes of ether. It melted at 120–121° on recrystallization from acetone.

7-(3-Azaspiro[5.5]undecan-3-yl)heptylamine.—The preceding aminonitrile (17.8 g., 0.068 mole) was reduced with 10 g. of lithium aluminum hydride in absolute ether, and on distillation yielded the product (13 g., 72%), b.p. 135–145° (0.3 mm.).

The **dihydrochloride** was obtained on adding 20 ml. of alcoholic HCl to the base in 25 ml. of isopropyl alcohol and diluting with 500 ml. of ether. It melted at 271–272° on recrystallization from methanol–ether.

3-[(4-*p*-Fluorophenyl-4-hydroxy)butyl]-3-azaspiro[5.5]undecane Hydrochloride.—3-[3-(*p*-Fluorobenzoyl)propyl]-3-azaspiro-[5.5]undecane (**9**) (7 g., 0.022 mole) was reduced with 1 g. of lithium aluminum hydride in absolute ether. After filtration of the inorganic material and drying the ether solution over Na_2SO_4, the ether was stripped off and all material boiling up to 100° (0.2 mm.) was distilled and discarded. The residue was dissolved in ether, filtered, and treated with gaseous HCl. The hydrochloride of the product melted at 226–227.5° on recrystallization from methanol–acetone. The infrared spectrum showed no carbonyl absorption and the presence of OH absorption.

3-[(*p*-Fluorophenylthio)propyl]-3-azaspiro[5.5]undecane.—*p*-Fluorothiophenol (6 g., 0.047 mole), 12.5 g. (0.047 mole) of 3-(3-azaspiro[5.5]undecan-3-yl)propyl chloride hydrochloride, and 4.2 g. of NaOH were refluxed for 8 hr. in 100 ml. of ethanol. The precipitated NaCl was filtered, the alcohol was distilled, and the residue was dissolved in ether and filtered. The ether was stripped, and the residue was distilled to give the product (12 g., 79%), b.p. 130–136° (0.3 mm.).

The **hydrochloride** was obtained by treating an ether solution of the base with gaseous HCl and melted at 231–232° on recrystallization from acetone.

3-[(3-*p*-Fluorophenylsulfonyl)propyl]-3-azaspiro[5.5]undecane Hydrochloride.—Sodium *p*-fluorophenyl sulfinate (9.2 g., 0.05 mole) and 11.5 g. (0.05 mole) of 3-(3-azaspiro[5.5]undecan-3-yl)propyl chloride were refluxed in a minimum (approximately 25 ml.) of dimethylformamide for 4 hr., cooled, diluted with four volumes of water, and kept in the refrigerator overnight. The oil that separated was dissolved in 10% HCl and washed with water and ether. The HCl solution was neutralized with 20% NaOH and extracted three times with 50 ml. of ether. The ether extract was washed with water, 10% $NaHCO_3$, water, and dried over Na_2SO_4. The ether solution was filtered and treated with gaseous HCl. The precipitate was filtered off, dissolved in ethanol, decolorized with charcoal, filtered, and reprecipitated with ether. It melted at 213–218°. After three recrystallizations from ethanol, there was obtained 13 g. (67%) of the title compound, m.p. 218–222°.

9-Methyl-3-[(3-*p*-fluorobenzoyl)propyl]-3,9-diazaspiro[5.5]-undecane.—9-Methyl-3,9-diazaspiro[5.5]undecane[6] (5 g., 0.03 mole) and 6 g. (0.03 mole) of 4-chloro-4′-fluorobutyrophenone were refluxed in 30 ml. of toluene containing 0.1 g. of KI for 8 hr. The solvents were stripped, the residue was treated with excess 10% NaOH, and extracted with ether. The ether extract was dried over Na_2SO_4, the ether was stripped, and the residue was distilled to give the product (6.7 g., 67%), b.p. 185–190° (0.1 mm.).

The **dihydrochloride,** obtained by treating an ether solution of the base with alcoholic HCl, melted at 284–286° dec. and at 285–287° dec. on recrystallization from ethanol–ether.