Spiranes. III.[1a,b] Azaspiranes and Intermediates[1c]

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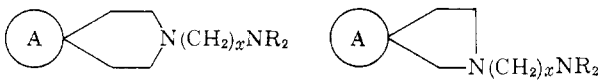
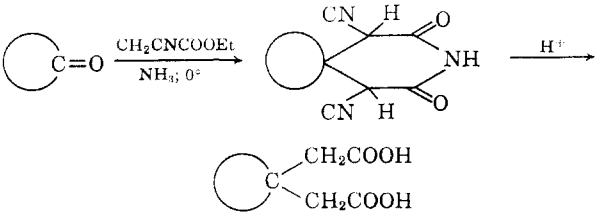
A large group of N-dialkylaminoalkyl azaspiroalkanes has been prepared and studied for physiological activity. Within this group of compounds, structural variations in the N-dialkylaminoalkyl substituent, azaspirane nuclei, and nuclear substituents were made. Of these compounds, several have shown marked effects on the growth of cancer cells *in vitro* and on reproduction in mammals. Many new intermediate Guareschi imides, cycloalkane or heterocycloalkane *gem*-diacetic and *gem*-carboxyacetic acids and anhydrides are described.

As part of a continuing study of heterocyclic ring systems, embracing primarily azabicyclic and azaspiro nuclei, containing a spiro carbon atom, we have prepared a rather extensive group of N-dialkylaminoalkyl substituted azaspiroalkanes. This interesting and important class of compounds has been only cursorily touched upon in the literature[2,3] and little is known concerning the biological effects of this type structure which has not been reported to occur in living organisms. In our studies, both the dialkylaminoalkyl substituent and azaspiroalkane ring portions of the basic structure have been extensively permutated to afford wide latitude in evaluating the physiological effects of these nuclei. Potent pharmacologic activity has been observed throughout the group of compounds studied. Of particular note are the marked growth inhibitory effects of certain members (*e.g.* ,3-(3-dimethylaminopropyl)-9-*t*-*t*butyl-3-azaspiro[5.5]undecane) on cancer cells in tissue culture and objective clinical effects in human cancer. Derivatives of the bicyclic systems related to naphthalene exhibited hormonal effects in mammals. One such derivative (spiro-*trans*-decalin-2,4′-piperidine-1′(3-dimethylaminopropyl)) produced effects which are grossly evident, in addition to histological changes, so far, in the production of dwarf offspring in a third generation of Wistar rats. This report is, therefore, divided into three sections consisting of summaries of (A) the chemistry of the compounds and their intermediates, (B) pharmacological activity, and (C) clinical observations.

A. Chemical.—Those compounds prepared and studied are represented by the general formulas



where ring A is attached to the 4-position of a piperidine ring or the 3-position of a pyrrolidine ring. In all cases, it is to be noted, the nitrogen is removed by at least one carbon atom from the spiro carbon. When the ring is piperidine, methods have been worked out to introduce substituents at the 1,5-positions of the azaspirane moiety. The ring A has been varied from a simple carbocyclic ring of 5 to 8 carbon atoms to bicyclic rings such as decalin and hydrindane. In addition, sulfur or oxygen has been introduced into ring A to produce a tetrahydrothiophene, tetrahydrothiapyrane, or tetrahydropyrane containing system. The basic ring systems prepared and utilized are shown in Chart I where the hydrogen is replaced by a dialkylaminoalkyl grouping. A variety of substituents such as methyl, cyclohexyl, methoxy, and butyl have been incorporated into ring A. The necessary intermediates for this study were the *gem*-cycloalkanediacetic acids and cycloalkanecarboxyacetic acids. *gem*-Diacetic acids were prepared by the general method shown in the sequence



In the series of reactions above, the ketone was treated at 0° with an excess of ammonia in ethanol and

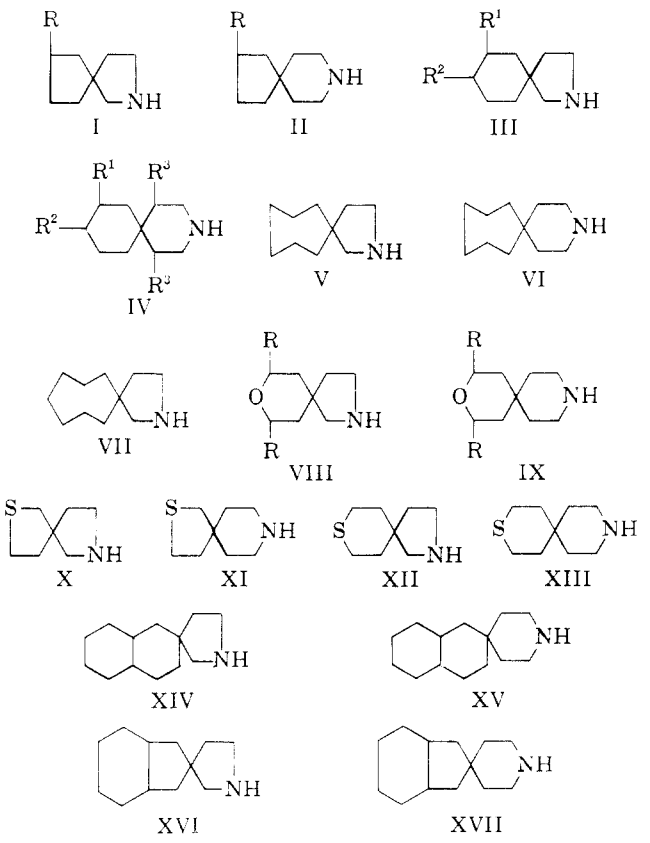


Chart I

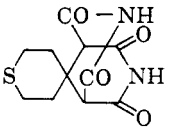
(1) (a) J. B. Clements and L. M. Rice, *J. Org. Chem.*, **24**, 1958 (1959); (b) L. M. Rice and C. H. Grogan, *ibid.*, **26**, 54 (1961); (c) this work was supported by the Geschickter Fund for Medical Research, Inc.; (d) to whom requests for reprints should be directed at the Dietene Co., Minneapolis, Minn.

(2) J. Boeseken, *Traité Chim. Org.*, **17**, 1787 (1949).

(3) K. Thomae, British Patent 823,338 (1959).

2 moles of ethyl cyanoacetate to yield the ammonium salt of the Guareschi imide.[4] After dissolving the salt in water, the Guareschi imide was precipitated by acidifying with hydrochloric acid. These Guareschi imides are listed in Table XV and presented no particular preparative difficulty except in the wide variations in solubility exhibited by various members. For example, the ammonium salts of the Guareschi imides from 4-cyclohexylcyclohexanone and 4-*t*-butylcyclohexanone were not very soluble in hot water, whereas the product from 2,6-dimethyltetrahydropyrone-4 was extremely soluble. The products from the heterocyclic ketones were fairly soluble in water, and care had to be taken to dissolve them in a minimum amount of water prior to precipitation. These details are presented more fully in the Experimental section.

Hydrolysis of the individual dicyanoimides to the desired *gem*-diacids using the general procedure of Kon and Thorpe,[4a] employing 60% sulfuric acid, caused considerable difficulty because of the solubility and stability differences of the various ring systems in this medium. Solubility differences were most evident in the cases of bulky substituents, such as *t*-butyl and cyclohexyl on IV, Chart I. In these cases, the concentration of acid had to be increased. Stability problems were encountered in those imides in which oxygen or sulfur had replaced one of the carbon atoms as in IX, XI, and XIII, Chart I. These rings showed extensive cleavage under the conditions of the sulfuric acid hydrolysis. This was overcome by treatment of the Guareschi imide with alkali as proposed by Kerr[5] in his elegant research on norpinic acid. By this method, the corresponding acids were isolated in poor yield. Several attempts to modify this procedure either gave no product or approximately the same small yield. Later in one case (XIII) it was found that prolonged boiling of the Guareschi imide with concentrated hydrochloric acid gave an improved yield of hydrolysis product. In the course of this reaction, we have isolated a product which we believe to be the internal imide of 9-thia-3-azaspiro[5:5]undecane-2,4-dione of the structure



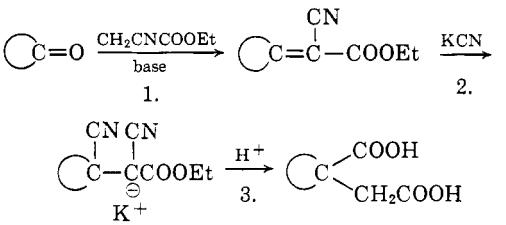
We have tentatively assigned this structure based on solubility, infrared, and elemental analysis. This compound is described more fully in the Experimental section. The procedure was not tried on the Guareschi imides corresponding to IX and XI, Chart I, or the dicyano imide from 4-methoxycyclohexanone. We believe that an improved yield would also be obtained in these cases. These new acids are listed in Table XVI. They were converted by means of acetic anhydride to their anhydrides, which are also listed with appropriate constants in Table XVI. In some cases where the quantity of anhydride was small, the product was used without further purification for further synthetic steps.

(4) (a) G. A. R. Kon and J. F. Thorpe, *J. Chem. Soc.*, **115**, 701 (1919); (b) F. B. Thole and J. F. Thorpe, *ibid.*, **99**, 445 (1915); (c) I. Guareschi, *Atti Accad. Sci. Torino*, **36**, 443 (1900/1901).

(5) C. A. Kerr, *J. Am. Chem. Soc.*, **51**, 618 (1929).

The introduction of methyl groups at the 1,5-positions of the spirodicyanoimide on the same carbon which was substituted by nitrile was achieved by alkylation of the Guareschi imide with methyl iodide in the presence of sodium methoxide. In this case, three methyl groups entered the cyanoimide at the 1,3,5-positions. Hydrolysis of the trimethyl imide in the usual manner gave the desired cyclohexane-α,α'-dimethyl-1,1-diacetic acid.

The necessary cycloalkane-1-carboxy-1-acetic acids were prepared as illustrated in the following reaction sequence. Step 1 consisted in the base catalyzed



condensation of the ketone with one mole of ethyl cyanoacetate to yield the corresponding cycloalkylidene cyanoacetic ester. In general piperidine[6] was a satisfactory catalyst with the majority of the ketones. However, in cases where the piperidine catalyzed condensation failed, the ketone was expensive or hindered, and maximum yield was desired, the alternative procedure of Cope[7] employing ammonium acetate was more satisfactory. Neither method effected the condensation of camphor or 3,3,5-trimethylcyclohexanone. In all other cases studied, satisfactory yields were obtained by one or both of the methods. The cycloalkylidene cyanoacetic esters, together with appropriate constants, are listed in Table XVII. These compounds were stable for varying periods following their isolation in the pure state. However, in many cases they became discolored on standing at room temperature (slower at 0–5°) and an increasingly strong odor of hydrogen cyanide was noted. They were, therefore, generally treated with sodium or potassium cyanide in aqueous alcohol within a short time after preparation.

Step 2 consisted in the addition of alkali metal cyanide across the double bond of the alkylidene ester. This addition proceeded readily. Several attempts to isolate the addition product in pure form failed. However, this isolation attempt was not pursued in great detail.

Direct hydrolysis of the crude product, obtained by removal of solvents, with concentrated hydrochloric acid yielded the desired acid in all cases (Table XVIX). Dehydration of the acids by means of acetic anhydride proceeded readily and the products were isolated by vacuum distillation.

The azaspiranediones were prepared by the reaction of an anhydride of a *gem*-substituted cycloalkane-1,1-diacetic acid or a cycloalkane-1-carboxy-1-acetic acid with the appropriate dialkylaminoalkylamine. This reaction proceeded exothermally to produce the amic acid which, when heated to a clear melt and maintained at 180–200°, readily split out water and cyclized to the spiroimide. The cyclization proceeded in high

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

(7) A. C. Cope, C. M. Hofman, C. Wyckoff, and E. Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

TABLE I

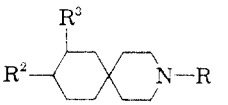
N-DIALKYLAMINOALKYL-3-AZASPIRO

	R	R^2	R^3	Formula	B.p., °C. (mm.)	Carbon, Calcd.	Carbon, Found
1.	2-Dimethylaminoethyl	H	H	$C_{14}H_{24}N_2O_2$	114–124 (0.1)	66.63	66.83
2.	3-Dimethylaminopropyl	H	H	$C_{15}H_{26}N_2O_2$	128–133 (0.15)	67.63	67.85
3.	2-Diethylaminoethyl	H	H	$C_{16}H_{28}N_2O_2$	130–137 (0.05)	68.53	68.56
4.	3-Diethylaminopropyl	H	H	$C_{17}H_{30}N_2O_2$	155–165 (0.1)	69.34	69.07
5.	3-Dibutylaminopropyl	H	H	$C_{21}H_{38}N_2O_2$	179–190 (0.1)	71.95	71.86
6.	5-Diethylaminoamyl	H	H	$C_{19}H_{34}N_2O_2$	169–175 (0.2)	70.76	70.58
7.	5-Diethylamino-2-amyl	H	H	$C_{19}H_{34}N_2O_2$	155–161 (0.2)	70.76	70.54
8.	2-Piperidinoethyl	H	H	$C_{17}H_{28}N_2O_2$	147–152 (0.1)	69.82	69.81
9.	3-Morpholinopropyl	H	H	$C_{17}H_{28}N_2O_3$	173–176 (0.2)	66.21	66.41
10.	3-Pyrrolidinopropyl	H	H	$C_{17}H_{28}N_2O_2$	160–165 (0.2)	69.82	69.89
11.	3-Dimethylaminopropyl	H	CH_3	$C_{16}H_{28}N_2O_2$	132–136 (0.1)	68.53	68.67
12.	3-Dimethylaminopropyl	CH_3	H	$C_{16}H_{28}N_2O_2$	137–140 (0.2)	68.53	68.77
13.	3-Dimethylaminopropyl	$-C(CH_3)_3$	H	$C_{19}H_{34}N_2O_2$	155–165 (0.05)	70.76	70.66
14.	3-Dimethylaminopropyl	$-OCH_3$	H	$C_{16}H_{28}N_2O_3$	135–139 (0.15)	64.83	64.95
15.	3-Dimethylaminopropyl	C_6H_{11}	H	$C_{21}H_{36}N_2O_2$	190–200 (0.25)	72.37	72.05
16.	3-Morpholinopropyl	$-C(CH_3)_3$	H	$C_{21}H_{36}N_2O_3$	113–114[a]	69.19	69.55

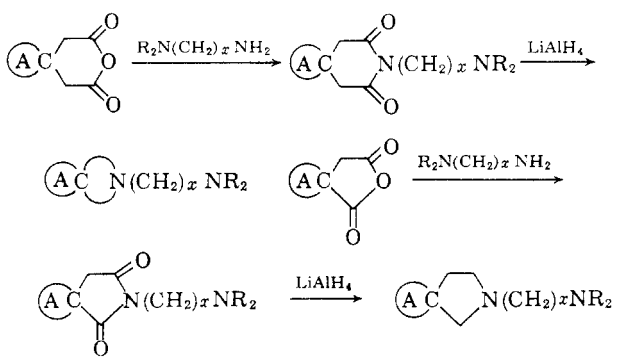
[a] M.p.

TABLE II

N-DIALKYLAMINOALKYL-3-AZASPIRO

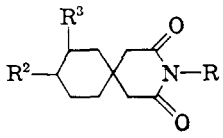


	R	R^2	R^3	Formula	B.p., °C. (mm.)	Carbon, Calcd.	Carbon, Found
1.	2-Dimethylaminoethyl	H	H	$C_{14}H_{28}N_2$	76–80 (0.075)	74.94	74.94
2.	3-Dimethylaminopropyl	H	H	$C_{15}H_{30}N_2$	85–95 (0.075)	75.56	75.81
3.	2-Diethylaminoethyl	H	H	$C_{16}H_{32}N_2$	88–93 (0.025)	76.12	76.17
4.	3-Diethylaminopropyl	H	H	$C_{17}H_{34}N_2$	103–106 (0.10)	76.62	76.81
5.	3-Dibutylaminopropyl	H	H	$C_{21}H_{42}N_2$	130–134 (0.05)	78.19	78.40
6.	5-Diethylaminoamyl	H	H	$C_{19}H_{38}N_2$	124–130 (0.075)	77.48	77.42
7.	5-Diethylamino-2-amyl	H	H	$C_{19}H_{38}N_2$	116–122 (0.05)	77.48	77.34
8.	2-Piperidinoethyl	H	H	$C_{17}H_{32}N_2$	110–114 (0.05)	77.21	77.00
9.	3-Morpholinopropyl	H	H	$C_{17}H_{32}N_2O$	121–125 (0.05)	72.80	73.03
10.	3-Pyrrolidinopropyl	H	H	$C_{17}H_{32}N_2$	103–113 (0.025)	77.21	77.47
11.	3-Dimethylaminopropyl	H	CH_3	$C_{16}H_{32}N_2$	86–88 (0.12)	76.12	76.36
12.	3-Dimethylaminopropyl	CH_3	H	$C_{16}H_{32}N_2$	95–98 (0.2)	76.12	76.30
13.	3-Dimethylaminopropyl	$C(CH_3)_3$	H	$C_{19}H_{38}N_2$	125–133 (0.025)	77.48	77.62
14.	3-Dimethylaminopropyl	OCH_3	H	$C_{16}H_{32}N_2O$	93–97 (0.05)		
15.	3-Dimethylaminopropyl	C_6H_{11}	H	$C_{21}H_{40}N_2$	150–160 (0.07)	78.68	78.54
16.	Morpholinopropyl	$C(CH_3)_3$	H	$C_{21}H_{40}N_2O$	160–170 (0.12)	74.94	74.21



yield. In several cases where solid imides were formed, these were obtained quantitatively. The spiroimides were reduced very smoothly in high yield by lithium aluminum hydride to the desired azaspiroalkane derivatives. These compounds were in general stable colorless oils which could easily be distilled under vacuum. A wide variety of amines were used and in all cases studied the reaction sequence was smooth. As evidenced by lack of by-products and high yield, the reaction proceeded in an almost quantitative manner. The basic azaspiroalkanes were then converted into suitable derivatives such as the hydrochlorides

(5.5) UNDECANE-2,4-DIONE

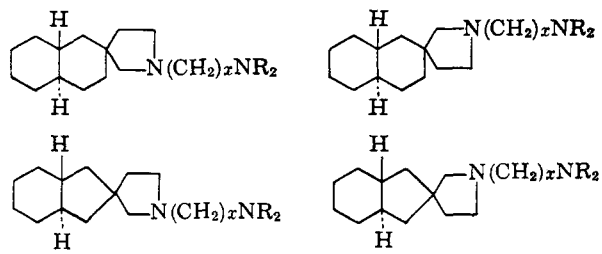


Analysis, % Hydrogen		Nitrogen		Methiodide M.p., °C.	Methiodide Analysis, % Iodide		Hydrochloride M.p., °C.	Hydrochloride Analysis, % Chlorine	
Calcd.	Found	Calcd.	Found		Calcd.	Found		Calcd.	Found
9.59	9.87	11.10	10.88	241–242	32.19	32.19	204–205	12.28	12.10
9.84	9.83	10.52	10.30	260–262	31.08	31.22	185–186	11.71	11.83
10.07	10.08	9.99	10.00	207–208	30.05	30.24	144–145	11.19	11.11
10.27	10.16	9.52	9.42	227–228	29.08	29.30	154–155	10.71	10.78
10.93	10.77	7.99	7.79	135–137	25.77	25.90	133–134	9.16	9.41
10.63	10.61	8.69	8.90	151–153	27.33	27.39	122–123	9.88	10.00
10.63	10.46	8.69	8.93	149–150	27.33	27.59	117–119	9.88	10.08
9.65	9.55	9.58	9.32	232–233	29.22	29.44	196–197	10.78	10.74
9.15	9.41	9.08	9.39	254–256	28.18	28.44	182–183	10.28	10.49
9.65	9.54	9.58	9.36	235–236	29.22	29.18	235–236	10.78	10.77
10.07	9.97	9.99	9.92	252–253	30.05	30.21	182–183	11.19	11.23
10.07	9.87	9.99	10.06	243–244	30.05	30.22	131–132	11.19	11.57
10.63	10.93	8.69	8.97	279–281	27.33	27.60	177–178	9.88	9.71
9.52	9.34	9.45	9.67						
10.41	10.15	8.04	8.36	258–259	25.88	25.85	164–165	9.21	9.21
9.95	10.05	7.69	7.50	249–250	25.06	24.93	237–238	8.84	8.62

(5.5) UNDECANE

Analysis, % Hydrogen		Nitrogen		Dimethiodide M.p., °C.	Dimethiodide Analysis, % Iodide		Dihydrochloride M.p., °C.	Dihydrochloride Analysis, % Chloride	
Calcd.	Found	Calcd.	Found		Calcd.	Found		Calcd.	Found
12.58	12.55	12.48	12.61	268–270	49.94	50.09	310–311	23.85	23.74
12.68	12.87	11.75	11.85	252–253	48.60	48.56	305–306	22.77	22.72
12.78	12.76	11.10	10.92	245–246	47.33	47.49	264–265	21.80	21.71
12.86	12.72	10.52	10.35	259–260	46.12	46.16	278–280	20.90	20.69
13.12	12.93	8.69	8.74	152–154	41.86	42.24	223–224	17.93	17.78
13.01	12.96	9.51	9.80	221–223	43.89	44.03	277–278	19.20	19.13
13.01	12.88	9.51	9.55	224–225	43.89	44.02	257–258	19.20	19.46
12.20	11.99	10.59	10.72	258–260	46.29	46.64	323–324	21.02	21.16
11.50	11.34	9.99	9.81	245–246	44.98	44.90	302–303	20.07	20.21
12.20	12.07	10.59	10.62	248–250	46.29	46.34	305–307	21.02	20.88
12.78	12.67	11.10	11.23	267–268	47.33	47.28	304–305	21.79	21.82
12.78	12.62	11.10	11.30	255–256	47.33	47.41	302–303	21.79	21.54
13.01	13.05	9.51	9.36	285–286	43.88	43.85	335–336	19.30	19.30
				245–246	45.96	45.74			
12.58	12.62	8.74	8.56	264–265	41.99	42.31	321–322	18.02	17.82
11.98	12.12	8.32	8.00	263–264	40.91	41.11	310–311	17.32	17.03

and methiodides for pharmacological testing. These were in most cases nice colorless crystalline compounds of high melting point (Tables I through XIV).

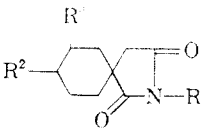


In the cases where the spiro compounds were prepared from *trans*-decalin-2-carboxy-2-acetic acid anhydride and *trans*-hydrindane-2-carboxy-2-acetic acid anhydride (structures XIV and XVI, Chart I, respectively) the formation of isomers probably took place. This was indicated by the lack of sharp melting points of some of the derivatives. No attempt was made to separate or determine the different configurations of these pairs in this study.[8] Although this was also possible in some of the other ring systems such as I or

(8) (a) K. A. N. Rao, *J. Chem. Soc.*, 1954 (1929); (b) J. Kandiah, *ibid.*, 923 (1931).

Table III

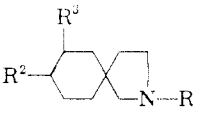
N-Dialkylaminoalkyl-2-azaspiro



	R	R^2	R^3	Formula	B.p., °C. (mm.)	Carbon, Calcd.	Carbon, Found
1.	2-Dimethylaminoethyl	H	H	$C_{13}H_{22}N_2O_2$	106–112 (0.05)	65.51	65.43
2.	3-Dimethylaminopropyl	H	H	$C_{14}H_{24}N_2O_2$	118–124 (0.075)	66.63	66.83
3.	2-Piperidinoethyl	H	H	$C_{16}H_{26}N_2O_2$	154–157 (0.25)	69.03	68.87
4.	3-Pyrrolidinopropyl	H	H	$C_{16}H_{26}N_2O_2$	146–154 (0.05)	69.03	68.95
5.	3-Morpholinopropyl	H	H	$C_{16}H_{26}N_2O_3$	160–165 (0.05)	65.28	65.16
6.	3-Dimethylaminopropyl	H	CH_3	$C_{15}H_{26}N_2O_2$	117–122 (0.25)	67.63	67.65
7.	3-Dimethylaminopropyl	CH_3	H	$C_{15}H_{26}N_2O_2$	115–117 (0.2)	67.63	67.86

Table IV

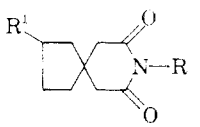
N-Dialkylaminoalkyl-2-azaspiro



	R	R^2	R^3	Formula	B.p., °C. (mm.)	Carbon, Calcd.	Carbon, Found
1.	2-Dimethylaminoethyl	H	H	$C_{13}H_{26}N_2$	80–82 (0.5)	74.22	74.30
2.	3-Dimethylaminopropyl	H	H	$C_{14}H_{28}N_2$	73–78 (0.1)	74.94	75.17
3.	2-Piperidinoethyl	H	H	$C_{16}H_{30}N_2$	95–105 (0.05)	76.74	77.00
4.	3-Pyrrolidinopropyl	H	H	$C_{16}H_{30}N_2$	99–103 (0.05)	76.74	76.85
5.	3-Morpholinopropyl	H	H	$C_{16}H_{30}N_2O$	113–122 (0.05)	72.13	72.38
6.	3-Dimethylaminopropyl	H	CH_3	$C_{15}H_{30}N_2$	82–84 (0.23)	75.57	75.73
7.	3-Dimethylaminopropyl	CH_3	H	$C_{15}H_{30}N_2$	78–80 (0.18)	75.57	75.83

Table V

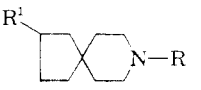
N-Dialkylaminoalkyl-8-azaspiro



	R	R^1	Formula	B.p., °C. (mm.)	Carbon, Calcd.	Carbon, Found
1.	2-Dimethylaminoethyl	H	$C_{13}H_{22}N_2O_2$	115–119 (0.075)	65.51	65.57
2.	3-Dimethylaminopropyl	H	$C_{14}H_{24}N_2O_2$	127–130 (0.075)	66.63	66.37
3.	2-Piperidinoethyl	H	$C_{16}H_{26}N_2O_2$	138–146 (0.075)	69.03	68.78
4.	3-Pyrrolidinopropyl	H	$C_{16}H_{26}N_2O_2$	144–148 (0.05)	69.03	69.23
5.	3-Morpholinopropyl	H	$C_{16}H_{26}N_2O_3$	166–173 (0.05)	65.28	65.57
6.	Dimethylaminopropyl	CH_3	$C_{15}H_{26}N_2O_2$	130–135 (0.2)	67.63	67.69

Table VI

N-Dialkylaminoalkyl-8-azaspiro



	R	R^1	Formula	B.p., °C. (mm.)	Carbon, Calcd.	Carbon, Found
1.	2-Dimethylaminoethyl	H	$C_{13}H_{26}N_2$	75–78 (0.20)	74.22	74.51
2.	3-Dimethylaminopropyl	H	$C_{14}H_{28}N_2$	88–94 (0.25)	74.94	75.04
3.	2-Piperidinoethyl	H	$C_{16}H_{30}N_2$	100–108 (0.05)	76.74	76.98
4.	3-Pyrrolidinopropyl	H	$C_{16}H_{30}N_2$	102–107 (0.05)	76.74	76.55
5.	3-Morpholinopropyl	H	$C_{16}H_{30}N_2O$	106–116 (0.03)	72.13	72.31
6.	3-Dimethylaminopropyl	CH	$C_{15}H_{30}N_2$	81–86 (0.25)	75.57	75.84

(4.5) DECANE-1,3-DIONES

Analysis, % Hydrogen		Nitrogen		Methiodides	Analysis, % Iodine		Hydrochlorides	Analysis, % Chlorine	
Calcd.	Found	Calcd.	Found	M.p., °C.	Calcd.	Found	M.p., °C.	Calcd.	Found
9.31	9.22	11.76	11.74	194–195	33.38	33.20	210–211	12.90	12.78
9.59	9.60	11.10	11.33	176–177	32.19	32.33	177–178	12.28	12.25
9.41	9.20	10.06	10.39	199–200	30.19	30.18	185–186	11.26	11.17
9.41	9.43	10.06	10.21	132–133	30.19	30.20	234–235	11.26	11.22
8.90	8.75	9.52	9.71	187–188	29.09	29.09	197–198	10.72	10.60
9.84	9.95	10.52	10.57	118–120	31.08	30.79	172–173	11.71	11.51
9.84	9.98	10.52	10.20	135–136	31.08	31.07	194–196	11.71	11.87

(4.5) DECANES

Analysis, % Hydrogen		Nitrogen		Methiodides	Analysis, % Iodine		Hydrochlorides	Analysis, % Chlorine	
Calcd.	Found	Calcd.	Found	M.p., °C.	Calcd.	Found	M.p., °C.	Calcd.	Found
12.46	12.31	13.32	13.23	226–227	51.36	51.41	286–287	25.03	25.23
12.58	12.78	12.48	12.29	251–252	49.94	49.90	283–284	23.85	23.80
12.08	12.05	11.19	11.09	227–228	47.51	47.57	316–317	21.93	22.01
12.08	12.06	11.19	11.05	239–240	47.51	47.32	271–272	21.93	21.91
11.35	11.46	10.52	10.55	237–238	46.13	45.92	277–278	20.90	20.71
12.68	12.67	11.75	11.56	258–259	48.60	48.57	264–265	22.77	23.03
12.68	12.85	11.75	11.62	256–257	48.60	48.77	274–275	22.77	22.57

(4.5) DECANE-7,9-DIONES

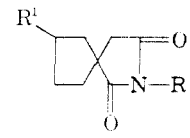
Analysis, % Hydrogen		Nitrogen		Methiodides	Analysis, % Iodine		Hydrochlorides	Analysis, % Chlorine	
Calcd.	Found	Calcd.	Found	M.p., °C.	Calcd.	Found	M.p., °C.	Calcd.	Found
9.31	9.35	11.76	11.67	188–189	33.38	33.29	189–190	12.90	12.96
9.59	9.58	11.10	11.20	254–255	32.19	32.35	145–146	12.28	12.25
9.41	9.60	10.06	9.81	181–182	30.19	30.32	179–180	11.26	11.41
9.41	9.63	10.06	10.15	178–179	30.19	30.42	224–225	11.26	11.37
8.90	8.95	9.52	9.40	237–238	29.09	29.40	196–197	10.72	10.62
9.84	9.81	10.52	10.69	266–267	31.08	31.25	156–157	11.71	11.74

(4.5) DECANES

Analysis, % Hydrogen		Nitrogen		Methiodides	Analysis, % Iodine		Hydrochlorides	Analysis, % Chlorine	
Calcd.	Found	Calcd.	Found	M.p., °C.	Calcd.	Found	M.p., °C.	Calcd.	Found
12.46	12.33	13.32	13.11	250–251	51.36	51.36	313–314	25.03	24.86
12.58	12.63	12.48	12.52	243–244	49.94	49.89	291–292	23.85	23.76
12.08	12.21	11.19	11.38	247–248	47.51	47.35	342–343	21.93	21.82
12.08	11.97	11.19	11.42	246–247	47.51	47.34	307–308	21.93	21.76
11.35	11.39	10.52	10.30	232–233	46.13	45.92	302–303	20.90	20.79
12.68	12.68	11.75	11.91	255–256	48.60	48.51	309–310	22.77	22.59

Table VII

N-Dialkylaminoalkyl-2-azaspiro

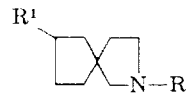


R	R¹	Formula	B.p., °C. (mm.)	Carbon, Calcd.	Carbon, Found
1. 2-Dimethylaminoethyl	H	$C_{12}H_{20}N_2O_2$	93–98 (0.05)	64.25	64.43
2. 3-Dimethylaminopropyl	H	$C_{13}H_{22}N_2O_2$	105–110 (0.05)	65.51	65.34
3. 3-Pyrrolidinopropyl	H	$C_{15}H_{24}N_2O_2$	143–151 (0.05)	68.15	68.06
4. 2-Piperidinoethyl	H	$C_{15}H_{24}N_2O_2$	143–148[a] (0.05)	68.15	68.36
5. 3-Morpholinopropyl	H	$C_{15}H_{24}N_2O_3$	163–168 (0.1)	64.26	64.49
6. 3-Dimethylaminopropyl	CH_3	$C_{14}H_{24}N_2O_2$	121–123 (0.3)	66.63	66.93
7. 3-Morpholinopropyl	CH_3	$C_{16}H_{26}N_2O_3$	153–158 (0.04)	65.28	65.16
8. 3-Diethylamino-2-hydroxypropyl	H	$C_{15}H_{26}N_2O_3$	143–146 (0.13)	63.80	64.07

[a] Melting point, 65–66°.

Table VIII

N-Dialkylaminoalkyl-2-azaspiro



R	R¹	Formula	B.p., °C. (mm.)	Carbon, Calcd.	Carbon, Found
1. 2-Dimethylaminoethyl	H	$C_{12}H_{24}N_2$	70–72 (0.45)	73.41	73.58
2. 3-Dimethylaminopropyl	H	$C_{13}H_{26}N_2$	92–95 (1.0)	74.22	74.36
3. 3-Pyrrolidinopropyl	H	$C_{15}H_{28}N_2$	94–99 (0.03)	76.21	76.36
4. 2-Piperidinoethyl	H	$C_{15}H_{28}N_2$	85–95 (0.03)	76.21	76.32
5. 3-Morpholinopropyl	H	$C_{15}H_{28}N_2O$	103–108 (0.1)	71.38	71.67
6. 3-Dimethylaminopropyl	CH_3	$C_{14}H_{28}N_2$	77–78 (0.1)	74.94	74.99
7. 3-Morpholinopropyl	CH_3	$C_{16}H_{30}N_2O$	93–98 (0.04)	72.13	72.17
8. 3-Diethylamino-2-hydroxypropyl	H	$C_{15}H_{30}N_2O$	90–91 (0.2)	70.81	71.02

[a] Hydrate.

III where R and R¹ are other than hydrogen and X, we believe that one form predominated and its structure corresponded to one of the two possible forms. We made no attempt to assign one of the two structures possible to our product in these cases. When the products were derived from the *gem*-diacetic acids, no isomerism of this type was possible.

B. Pharmacological Activity.—Although many of the compounds prepared displayed a variety of pharmacological activities, such as ganglionic blockage, produced dwarfed offspring in third generation of rats, etc., we were particularly interested in reporting on the antineoplastic activity of N-dimethylaminopropyl-9-*t*-butyl-3-azaspiro[5:5] undecane dihydrochloride. This compound when screened in the KB or He La cell tissue culture tests completely inhibited the cell growth at a concentration of 10^{-7}–10^{-9} g./ml.[9a] The activity in tissue culture was confirmed by two independent sources. The compound when evaluated in the cancer screen used at Georgetown University[9b] afforded 100% protection. This compound is stable and at a concentration of 50 mg./ml. has a pH of 5.3 and an I.P. single dose LD_{50} in rats of approximately 100 mg./kg.

(9) (a) *Cancer Chemotherapy Rept.*, I, 63 (1959); (b) C. F. Geschickter, I. A. Kamel, and E. P. Rubacky, *Georgetown Med. Bull.*, **14**, 193 (1961).

C. Clinical.—Because of the high activity in regard to inhibition of tissue cultures and in our animal screening procedure, we have carried out a study of 18 patients with severe carcinomas and sarcomas using N-dimethylaminopropyl-9-*t*-butyl-3-azaspiro[5:5]undecane. The drug was administered by the I.M., I.V. perfusion, and oral routes. These results are listed in Table XVIII.

Experimental[10]

Intermediate Ketones.—Most of the cyclopentanones, cyclohexanones, cycloheptanones, cyclooctanones, 2,6-dimethyl-γ-pyrone, and β-decalol were obtained from Columbia Organic Chemicals Co., Inc., Columbia, South Carolina. 4-Cyclohexylcyclohexanone[11] and 4-methoxycyclohexanone,[12] *trans*-hexahydro-β-hydrindone,[13] *trans*-β-decalone,[13] 3-ketotetrahydrothiophene,[14] and penthianone,[15] were prepared following the literature. Tetrahydro-γ-pyrone[16] was obtained by pyrolysis of

(10) All melting points were taken on a Thomas-Hoover melting point apparatus and are corrected.

(11) C. H. Shunk and A. L. Wilde, *J. Am. Chem. Soc.*, **71**, 3947 (1949).

(12) P. Ruggli, O. Leupin, and A. Businger, *Helv. Chim. Acta*, **24**, 339 (1941).

(13) R. J. Tudor and A. I. Vogel, *J. Chem. Soc.*, 1250 (1934).

(14) R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, **68**, 2229 (1946).

(15) G. M. Bennett and L. V. D. Scorah, *J. Chem. Soc.*, 194 (1927).

(16) (a) S. R. Cawley and S. G. P. Plant, *ibid.*, 1214 (1938); (b) R. Cornubert and P. Robinet, *Bull. Soc. Chim. France* [4] **53**, 565 (1933).

(4.4) NONANE-1,3-DIONES

Analysis, % Hydrogen		Nitrogen		Methiodides	Analysis, % Iodine		Hydrochlorides	Analysis, % Chlorine	
Calcd.	Found	Calcd.	Found	M.p., °C.	Calcd.	Found	M.p., °C.	Calcd.	Found
8.99	9.18	12.49	12.78	172–173	34.65	34.72	186–187	13.60	13.48
9.31	9.41	11.76	12.09	183–184	33.38	33.73	133–135	12.90	12.89
9.15	9.07	10.69	10.54	147–147.5	31.24	31.05	187–188	11.79	11.68
9.15	9.37	10.69	10.39	177–178	31.24	30.93	173–174	11.79	11.62
8.63	8.80	10.00	10.12	183–184	30.05	30.05	170–171	11.19	10.87
9.59	9.71	11.10	11.12	137–138	32.19	32.38	146–147	12.28	12.55
8.90	9.29	9.52	8.99	168–169	29.09	29.00	139–140	10.72	11.02
9.28	9.28	9.92	10.18	96–97	29.91	29.82	137–139	11.02	10.83

(4.4) NONANES

Analysis, % Hydrogen		Nitrogen		Methiodides	Analysis, % Iodine		Hydrochlorides	Analysis, % Chlorine	
Calcd.	Found	Calcd.	Found	M.p., °C.	Calcd.	Found	M.p., °C.	Calcd.	Found
12.32	12.55	14.27	14.00	228–230	52.86	52.97	273–274	26.34	26.04
12.46	12.22	13.32	13.12	247–248	51.36	51.49	264–265	25.03	24.67
11.94	11.97	11.85	11.61	235–236	48.79	48.54	246–247	22.93	22.97
11.94	12.05	11.85	11.75	236–237	48.79	48.47	306–307	22.93	22.70
11.18	11.35	11.10	10.83	219–220	45.80	45.99[a]	255–256	21.80	21.78
12.58	12.73	12.48	12.68	250–251	49.94	49.78	278–279	23.85	23.64
11.35	11.66	11.52	11.38	209–210	46.12	45.93	265–266	20.90	20.92
11.89	12.11	11.01	11.01				177–178	21.66	21.58

chelidonic acid followed by hydrogenation with 2% palladium on strontium carbonate. This catalyst was also used to hydrogenate 2,6-dimethyl-γ-pyrone and 6-methyl-2-phenyl-4-pyrone[17] to 2,6-dimethyltetrahydro-4-pyrone and 6-methyl-2-phenyltetrahydro-4-pyrone, respectively. In the 4-pyrones, if the hydrogenation product showed a considerable OH band on infrared examination, the product was reoxidized to the ketone.

Intermediate Acids.—The following acids used in this study had been prepared previously. 3-Methylcyclopentane-1,1-diacetic acid,[18-20] cyclopentane-1,1-diacetic acid,[4a,20] cyclopentane-1-carboxy-1-acetic acid,[6] 3-methylcyclopentane-1-carboxy-1-acetic acid,[18] cyclohexane-1,1-diacetic acid,[20,4b] 3-methylcyclohexane-1,1-diacetic acid,[21] 4-methylcyclohexane-1,1-diacetic acid,[20,21] cyclohexane-1-carboxy-1-acetic acid,[6] cycloheptane-1,1-diacetic acid,[22] cycloheptane-1-carboxy-1-acetic acid,[6] cyclooctane-1-carboxy-1-acetic acid,[23] *trans*-decahydronaphthalene-2,2-diacetic acid,[8a,20] *trans*-decahydronaphthalene-2-carboxy-2-acetic acid,[6,8a] and *trans*-hexahydrohydrindene-1-carboxy-1-acetic acid.[8b]

The general procedure for preparing most of the azaspiroalkanes was carried out in essentially the same manner; therefore, one detailed example is given which applies to most of the intermediate compounds listed in the Tables. Individual cases in which substantial changes were incorporated and the intermediates were new are detailed.

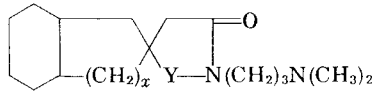
(17) S. Ruhemann, *J. Chem. Soc.*, **93**, 431 (1908).
(18) R. D. Desai, *ibid.*, 1220 (1931).
(19) A. I. Vogel, *ibid.*, 913 (1931).
(20) A. I. Vogel, *ibid.*, 1758 (1934).
(21) J. F. Thorpe and A. S. Wood, *ibid.*, **103**, 1597 (1913).
(22) G. A. R. Kon, *ibid.*, **117**, 639 (1920).
(23) D. Scheurer and O. Schlichting, British patent 828,753 (1960).

N-Dimethylaminopropyl-3-azaspiro[5:5]undecane-2,4-dione.—To 20 g. (0.101 mole) of powdered cyclohexane-1,1-diacetic acid anhydride contained in a small flask was added 11.7 g. (excess) of dimethylaminopropylamine with shaking. The reaction was exothermic. A little heat was applied if necessary to obtain a clear melt and the mixture was heated at 180–200° for 1 hr. Rapid evolution of water was observed. After this time, the cyclization of the amic acid to the imide was complete as evidenced by the lack of formation of water. The crude product was allowed to cool and distilled *in vacuo*. The pure product was collected as a colorless oil, b.p. 128–133° (0.15 mm.), and weighed 26.8 g. (91.5%). The methiodide was made by adding an excess of methyl iodide to an acetone solution of the base and melted at 260–262°. Recrystallization from 2-propanol and methanol did not change the melting point. The hydrochloride was prepared by adding a slight excess of alcoholic hydrogen chloride to the base dissolved in alcohol. It melted at 185–186° and did not change on recrystallization.

N-Dimethylaminopropyl-3-azaspiro[5:5]undecane.—Lithium aluminum hydride (15 g.) and 1 l. of anhydrous ether were placed into a 2-l., 3-necked flask, fitted with a stirrer, dropping funnel, and reflux condenser and protected from moisture. When solution was effected, a solution of 20 g. of N-dimethylaminopropyl-3-azaspiro[5:5]undecane-2,4-dione dissolved in 200 ml. of anhydrous ether was added over a period of 15 min. The reaction mixture was stirred for 3 hr. and then decomposed by the slow dropwise addition of water. A slight excess of water was added, the inorganic solids were filtered off, the ethereal solution was dried over sodium sulfate and the ether was removed. The resultant oil was distilled *in vacuo* to yield 15.8 g. of base boiling at 85–95° (0.075 mm.). The **dihydrochloride** of the base was prepared by treating a 2-propanol solution of the base with

TABLE IX

N-DIMETHYLAMINOPROPYL-AZASPIRODIONE COMPOUNDS FROM BICYCLIC SYSTEM

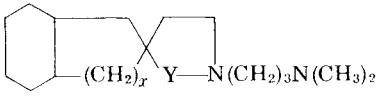


					Analysis, %						Methiodides			Hydrochlorides		
					Carbon		Hydrogen		Nitrogen			Analysis, % Iodine			Analysis, % Chlorine	
	x	Y	Formula	B.p., °C. (mm.)	Calcd.	Found	Calcd.	Found	Calcd.	Found	M.p., °C.	Calcd.	Found	M.p., °C.	Calcd.	Found
1.	1[a]	—CO—	$C_{17}H_{28}N_2O_2$	142–146 (0.1)	69.82	69.99	9.65	9.69	9.58	9.88	234–235	29.22	29.42	216–217	10.78	11.07
2.	1[a]	—CH_2CO—	$C_{18}H_{30}N_2O_2$	153–157 (0.1)	70.55	70.57	9.87	9.82	9.14	8.81	245–246	28.31	28.60	222–224	10.34	10.19
3.	2[b]	—CO—	$C_{18}H_{30}N_2O_2$	138–148 (0.02)	70.55	70.83	9.87	9.68	9.14	9.13	[c]	[c]	[c]	[c]	[c]	[c]
4.	2[b]	—CH_2CO—	$C_{19}H_{32}N_2O_2$	170–178[d] (0.02)	71.21	71.48	10.07	9.96	8.74	8.60	244–245	27.45	27.45	167–168	9.93	9.90

[a] *trans*-Hydrindanyl. [b] *trans*-Decalyl. [c] Melted over range. A mixture of isomers. [d] M.p. 59–60°.

TABLE X

N-DIMETHYLAMINOPROPYL-AZASPIRO COMPOUNDS FROM BICYCLIC SYSTEM

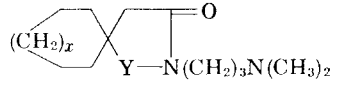


					Analysis,%						Dimethiodide			Dihydrochloride		
					Carbon		Hydrogen		Nitrogen			Analysis, % Iodine			Analysis, % Chlorine	
	x	Y	Formula	B.p., °C. (mm.)	Calcd.	Found	Calcd.	Found	Calcd.	Found	M.p., °C.	Calcd.	Found	M.p., °C.	Calcd.	Found
1.	1[a]	—CH_2—	$C_{17}H_{32}N_2$	112–115 (0.1)	77.21	77.53	12.20	11.98	10.59	10.74	246–247	46.29	46.34	283–284	21.02	21.11
2.	1[a]	—CH_2CH_2—	$C_{18}H_{34}N_2$	[c]	77.63	77.58	12.31	12.42	10.06	10.16	285–186	45.14	45.20	327–328	20.18	20.12
3.	2[b]	CH_2—	$C_{18}H_{34}N_2$	120–122 (0.2)	77.63	77.31	12.31	12.43	10.06	10.30	[d]	45.14	45.01	[d]	20.18	20.07
4.	2[b]	CH_2CH_2	$C_{19}H_{36}N_2$	124–129 (0.05)	78.02	78.21	12.41	12.56	9.58	9.50	279–280	44.04	43.91	319–320	19.41	19.20

[a] *trans*-Hydrindanyl. [b] *trans*-Decalyl. [c] Quantity too small. [d] No definite melting point. Probably a mixture of isomers.

TABLE XI

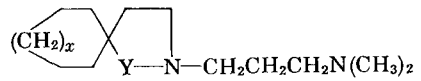
DIMETHYLAMINOPROPYL-X-AZASPIROALKANEDIONES



					Analysis, %						Methiodide			Hydrochloride		
					Carbon		Hydrogen		Nitrogen			Analysis, % Iodine			Analysis, % Chlorine	
	x	Y	Formula	B.p., °C. (mm.)	Calcd.	Found	Calcd.	Found	Calcd.	Found	M.p., °C.	Calcd.	Found	M.p., °C.	Calcd.	Found
1.	2	—CO—	$C_{15}H_{26}N_2O_2$	133–135 (0.1)	67.63	67.55	9.84	9.75	10.52	10.59	193–194	31.08	31.12	187–188	11.71	11.57
2.	2	—CH_2CO—	$C_{16}H_{28}N_2O_2$	145–147 (0.08)	68.53	68.77	10.07	10.05	9.99	10.08	248–249	30.05	30.09	159–160	11.19	10.97
3.	3	—CO—	$C_{16}H_{28}N_2O_2$	134–136 (0.1)	68.53	68.79	10.07	10.18	9.99	10.00	199–200	30.05	30.00	173–174	11.19	11.20

TABLE XII

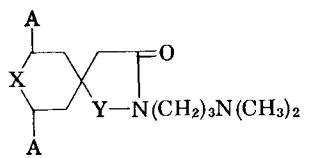
DIMETHYLAMINOPROPYL-X-AZASPIROALKANES



					Analysis, %						Dimethiodide			Dihydrochloride		
					Carbon		Hydrogen		Nitrogen		Analysis, % Iodine			Analysis, % Chlorine		
	x	Y	Formula	B.p., °C. (mm.)	Calcd.	Found	Calcd.	Found	Calcd.	Found	M.p., °C.	Calcd.	Found	M.p., °C.	Calcd.	Found
1.	2	—CH_2—	$C_{15}H_{30}N_2$	83–89 (0.05)	75.56	75.57	12.68	12.70	11.75	12.04	257–258	48.60	48.59	280–281	22.77	22.56
2.	2	—CH_2CH_2—	$C_{16}H_{32}N_2$	108–113 (0.1)	76.12	76.19	12.78	12.68	11.10	11.16	258–259	47.32	47.17	309–310	21.80	21.75
3.	3	—CH_2—	$C_{16}H_{32}N_2$	94–96 (0.1)	76.12	76.12	12.78	12.78	11.10	11.39	254–255	47.32	47.42	286–288	21.80	21.72

TABLE XIII

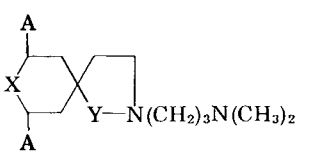
N-DIMETHYLAMINOPROPYL-AZASPIROHETEROALKANODIONES



						Analysis, %						Methiodides			Hydrochlorides		
						Carbon		Hydrogen		Nitrogen		Analysis, % Iodine			Analysis, % Chlorine		
	X	Y	A	Formula	B.p., °C. (mm.)	Calcd.	Found	Calcd.	Found	Calcd.	Found	M.p., °C.	Calcd.	Found	M.p., °C.	Calcd.	Found
1.	O	—CO—	CH_3	$C_{15}H_{26}N_2O_3$	124–128 (0.05)	63.80	63.94	9.28	9.58	9.92	10.07	184–185	29.91	29.62	197–198	11.12	10.85
2.	O	—CH_2—CO—	CH_3	$C_{16}H_{28}N_2O_3$	136–142 (0.02)	64.83	64.61	9.52	9.52	9.45	9.35	266–267	28.95	29.11	163–164	10.65	10.78
3.	S	—CO—	H	$C_{13}H_{22}N_2O_2S$	141–146 (0.025)	57.74	57.90	8.20	8.32	10.36	10.28				199–200	11.56	11.68

TABLE XIV

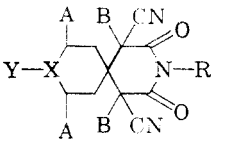
N-DIMETHYLAMINOPROPYL-AZASPIROHETEROALKANES

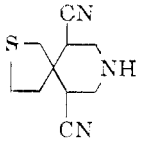


						Analysis, %						Dimethiodide			Dihydrochloride		
						Carbon		Hydrogen		Nitrogen		Analysis, % Iodine			Analysis, % Chlorine		
	X	Y	A	Formula	B.p., °C. (mm.)	Calcd.	Found	Calcd.	Found	Calcd.	Found	M.p., °C.	Calcd.	Found	M.p., °C.	Calcd.	Found
1.	O	—CH_2—	CH_3	$C_{15}H_{30}N_2O$	89–92 (0.05)	70.81	70.70	11.89	11.75	11.01	11.15	261–262	47.15	46.89	283–284	21.66	21.37
2.	O	—CH_2CH_2—	CH_3	$C_{16}H_{32}N_2O$	98–101 (0.02)	71.59	71.65	12.02	11.98	10.44	10.53	279–280	45.96	46.02	294–295	20.77	21.00
3.	S	—CH_2—	H	$C_{13}H_{26}N_2S$	97–103 (0.025)	64.41	64.33	10.81	10.60	11.56	11.90				280–281	22.48	22.55

TABLE XV

GUARESCHI IMIDES



	Y	X	A	B	R	Formula	M.p., °C.	Analysis, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1.	H_3CO	CH	H	H	H	$C_{13}H_{16}N_2O_3$	186–187	59.76	60.01	5.74	6.04	16.08	16.31
2.	$(CH_3)_3C$	CH	H	H	H	$C_{16}H_{24}N_2O_2$	244–245	66.88	66.87	7.37	7.22	14.63	14.38
3.	C_6H_{11}	CH	H	H	H	$C_{18}H_{28}N_2O_2$	225–226	68.98	69.11	7.40	7.59	13.41	13.57
4.		O	CH_3	H	H	$C_{13}H_{16}N_2O_3$	231–232	59.76	59.91	5.79	6.08	16.08	15.93
5.		S	H	H	H	$C_{11}H_{12}N_2O_2S$[a]	208–210	52.99	52.93	4.45	4.49	16.86	16.60
6.		CH_2	H	CH_3	CH_3	$C_{16}H_{19}N_2O_2$	166–167	65.91	66.05	7.01	6.83	15.37	15.27
7.						$C_{10}H_9N_3O_2S$	221–222	51.05	50.92	3.86	4.03	17.86	17.92

[a] Calcd.: S, 12.86. Found: S, 12.60.

ethanolic hydrogen chloride and precipitating with absolute ether. After recrystallization, it melted at 305–306°. The **dimethiodide** was prepared by refluxing an alcohol solution of the base with an excess of methyl iodide. Ethyl acetate was added until crystallization started and after cooling, the product was filtered. It melted at 252–253°.

N-Morpholinopropyl-9-*t*-butyl-3-azaspiro[5:5]undecane-2,4-dione.—This compound was prepared in 98% yield as indicated in the general method given above except that the product crystallized on cooling and distillation was omitted. The product after recrystallization from ligroin melted at 113–114°.

N-Morpholinopropyl-9-*t*-butyl-3-azaspiro[5:5]undecane.—This compound was prepared by reduction of the dione as given in the general method. The product had a boiling point of 160–170° (0.12 mm.). The yield was 91%.

The Guareschi Imide-9-*t*-butyl-1,5-dicyano-3-azaspiro[5:5]-undecane-2,4-dione.—A mixture of 154 g. (1 mole) of 4-*t*-butylcyclohexanone dissolved in 200 ml. of alcohol and 226 g. (2 moles) of ethyl cyanoacetate, contained in a wide-mouthed bottle, was cooled to 0°. To this mixture was added 600 ml. of absolute alcohol previously saturated at 0° with anhydrous ammonia. (When 600 ml. of alcohol is saturated with ammonia, the volume expands to roughly 900 ml. Thus, 900 ml. was used.) The bottle was stoppered and the top wired or taped down. After sitting for 5–7 days in the cold (below 5°), the separated ammonium salt of the dicyanoimide was filtered off, pressed, and washed several times with alcohol. After the filter cake had stopped dripping, the solid ammonium salt (240 g.) was dissolved in a large volume of boiling water. For every 120 g. of dry product, 6 l. of water was used. The solution contained much insoluble matter which was removed by filtration while keeping the filtrate hot. The hot solution was stirred and acidified with concd. hydrochloric acid, and a 200 ml. excess added. After allowing the mixture to cool, the product was filtered off and washed several times with water. After drying, it weighed 51 g. and melted at 235–240°. From the 240 g. of above salt, a total of 102 g. of free imide was obtained. On recrystallization from alcohol and then methanol, the product melted at 244–245°.

4-*t*-Butylcyclohexane-1,1-diacetic Acid.—The above dry Guareschi imide (100 g.) was powdered and dissolved in 400 ml. of concd. sulfuric acid using a 3-l. flask. After standing overnight, 280 ml. of water was added with frequent shaking. The mixture was heated under reflux for 12–20 hr. with intermittent shaking until frothing had ceased. After the mixture was allowed to cool to room temperature, 1 l. of water was added with stirring. The crude acid together with some charred material was filtered off on a sintered glass funnel and washed well with water. The crude reaction product was then suspended in 3 l. of hot water and sufficient potassium bicarbonate was added to dissolve all of the acid. After boiling with charcoal, the solution was filtered and the filtrate acidified with concd. hydrochloric acid. The precipitate was filtered off, washed with water, and dried at 100°. It melted at 181–184°. Recrystallization from ethyl acetate–petroleum ether gave the pure acid melting at 183–184°. The yield was 65%.

4-*t*-Butylcyclohexane-1,1-diacetic Acid Anhydride.—The acid was mixed with 3 times its weight of acetic anhydride and refluxed for 3 hr. Excess acetic anhydride was removed under reduced pressure and the residue was distilled *in vacuo*. The product boiled at 156–162° (0.1 mm.) and solidified in the receiver. Recrystallization from hexane afforded material melting at 110–111°.

Ethyl 4-*t*-Butylcyclohexylidene Cyanoacetate.—A mixture of 154 g. (1 mole) of 4-*t*-butylcyclohexanone and 113 g. (1 mole) of ethyl cyanoacetate was heated until homogeneous and 2 ml. of piperidine was added. The mixture was allowed to stand 1 week. Every morning the reaction was heated to boiling and allowed to cool. After this period, the mixture was distilled and the fraction boiling at 119–121° (0.25 mm.) was collected. The product (199 g., 79.8%) solidified in the receiver and on recrystallization from hexane melted at 41–42°.

4-*t*-Butylcyclohexane-1-carboxy-1-acetic Acid.—The above cyanoester (192 g.) was dissolved in 720 ml. of alcohol and a solution of 102 g. of potassium cyanide in 215 ml. of water was added. After standing for 5 days with occasional shaking, the solvent was removed under reduced pressure. The mixture was transferred to the hood and 1 l. of concd. hydrochloric acid was slowly added with shaking. After refluxing for 24 hr., the reaction mixture was allowed to cool and diluted with an equal volume of water. After filtering and washing with water, the crude acid was dissolved in potassium bicarbonate and was treated with charcoal. The filtered solution was acidified with concd. hydrochloric acid and the product was collected. This material was suitable for conversion to the anhydride employing acetic anhydride as outlined above for the corresponding diacetic acid derivative. **Anhydride:** m.p. 112–113°; b.p. 138–142° (0.25 mm.). **Acid:** The anhydride was hydrolyzed with 2 *N* sodium hydroxide at reflux. After acidifying, filtering, and recrystallization from ethyl acetate–ligroin, the pure acid melted at 191–192°.

4-Cyclohexylcyclohexane-1,1-diacetic Acid.—A solution of 125 g. of 4-cyclohexylcyclohexanone in 158 g. of ethyl cyanoacetate was cooled to 0° and mixed with 1 l. of absolute alcohol that had been saturated with ammonia at 0°. The stopper was wired down and the precipitate was filtered after 1 week. The filter cake was washed with alcohol followed by ether and sucked dry. After dissolving the ammonium salt in a large volume of hot water and filtering, the solution was acidified and cooled and the precipitate then filtered, washed, and dried. The product weighed 144 g. and melted at 225–226°. Hydrolysis was effected by dissolving 140 g. of the above imide in 600 ml. of concd. sulfuric acid and, after standing overnight, diluting with water (470 ml.) to make a 70% w./w. sulfuric acid concentration. The mixture was refluxed with occasional shaking for 24 hr. There was considerable charring in the process. Water (2 volumes) was added, the mixture was allowed to cool, and was filtered and washed. The crude product was boiled with a large volume of potassium

TABLE XVI

CYCLOALKANE-1,1-DIACETIC ACIDS AND ANHYDRIDES

							Analysis, %				Anhydrides		Analysis, %			
							Carbon		Hydrogen				Carbon		Hydrogen	
	Y	X	A	B	Formula	M.p., °C.	Calcd.	Found	Calcd.	Found	B.p., °C. (mm.)	M.p., °C.	Calcd.	Found	Calcd.	Found
1.	CH_3O	CH	H	H	$C_{11}H_{18}O_5$	154–155	57.38	57.48	7.88	7.66	135–145 (0.2)	63–65	62.25	62.17	7.60	7.52
2.	$(CH_3)_3C$	CH	H	H	$C_{14}H_{24}O_4$	183–184	65.86	66.18	9.08	9.22	156–162 (0.1)	110–111	70.56	70.83	9.31	9.47
3.	C_6H_{11}[a]	CH	H	H	$C_{16}H_{26}O_4$	197–198	68.05	68.29	9.28	9.50	180–190 (0.3)	102–105.5	72.69	73.05	9.15	9.36
4.		O	CH_3	H	$C_{11}H_{18}O_5$	155–156	57.38	57.56	7.88	8.16	132–137 (0.04)	110–111	62.25	62.13	7.60	7.59
5.		S	H	H	$C_9H_{14}O_4S$[b]	174–175	49.52	49.67	6.46	6.52						
6.	H	CH	H	CH_3	$C_{12}H_{20}O_4$[c]	143–145	63.13	63.24	8.83	8.72	106–107 (0.5)	60–61	68.54	68.41	8.63	8.45
7.		S	CH_2COOH	H	$C_8H_{12}O_4S$	159–160	47.04	46.85	5.92	5.83						
			CH_2COOH													

[a] Cyclohexyl. [b] Sulfur: Calcd.: 14.69; Found: 14.44. [c] Calcd. acid equiv.: 114; Found: 113.

bicarbonate solution and treated with charcoal. The solution was filtered and reprecipitated with hydrochloric acid. This crude acid was filtered, washed with water, and dried. Conversion to the anhydride was effected by refluxing with acetic anhydride for several hours. Removal of the excess acetic anhydride under vacuum and distillation of the residue afforded the anhydride which boiled at 180–190° (0.3 mm.) and melted at 102.5–103.5°. Hydrolysis of a small portion of the above anhydride with 2 *N* sodium hydroxide and acidification yielded the pure acid which melted at 197–198° on recrystallization from ethyl acetate–ligroin.

4-Methoxycyclohexane-1,1-diacetic Acid.—A solution of 116 g. of 4-methoxycyclohexanone (1 mole) in ethyl cyanoacetate (2 moles) was prepared and cooled to 0°. Alcohol (600 ml.) was saturated with ammonia at 0° and this solution was added to the solution containing the ketone. The resulting solution was kept at 0° for 1 week, filtered, and washed with a small amount of cold 2-propanol followed by ether. After drying, the ammonium salt (126 g.) was dissolved in a minimum amount of warm water, cooled, and acidified to pH 1 with concd. hydrochloric acid. The product was filtered, washed with ice water, and dried; yield, 60 g. This imide is fairly soluble in water and hydrochloric acid. Recrystallization from 2-propanol yielded pure compound that melted at 186–187°.

In a number of attempts, hydrolysis of this imide with sulfuric acid was unsuccessful. The hydrolysis was successfully accomplished in low yield by the following method patterned after Kerr.[5] The imide (60 g.) was dissolved in 1 l. of 2.15% sodium hydroxide and refluxed for 2 hr. At the end of this time, the solution was concentrated on the steam bath to half its original volume, acidified with sulfuric acid, saturated with sodium sulfate, and extracted 6 times with ether. The ether was removed and the residue was refluxed with 10% sodium hydroxide for 10 hr. After cooling, the solution was acidified with sulfuric acid and extracted 10 times with ether. The ether was dried and removed by distillation and yielded a second residue which was decarboxylated at 200° and then refluxed with acetic anhydride and distilled. The crude anhydride was hydrolyzed with 2 *N* sodium hydroxide and acidified. Continuous ether extraction yielded 3 g. of acid which after petroleum ether recrystallization melted at 154–155°. As an alternative, the residue above from the 2.15% sodium hydroxide was boiled overnight with concd. hydrochloric acid and then evaporated to dryness. Preparation of the anhydride and hydrolysis with sodium hydroxide yielded the same acid.

1,3,5-Trimethyl-1,5-dicyano-3-azaspiro[5:5]undecane-2,4-dione.—To a solution of 13.8 g. (0.6 mole) of sodium dissolved in 1 l. of methanol was added 46.2 g. (0.2 mole) of the Guareschi imide from cyclohexanone (1,5-dicyano-3-azaspiro[5:5]undecane-2,4-dione). The imide dissolved immediately and the mixture was refluxed for 0.5 hr. Methyl iodide (114 g., 0.8 mole) was added slowly and refluxing was continued for an additional 2 hr. After standing overnight, the reaction mixture was poured with stirring into 1 l. of water containing 100 ml. of nitric acid. The product separated, was filtered, and washed with dilute alcohol. When dry, the material was dissolved in methanol, treated with charcoal, filtered, and allowed to crystallize. The crude product weighed 26 g. and melted at 161–163°. One recrystallization from methanol raised the melting point to 166–167°. It was unchanged on further recrystallization. The infrared spectrum showed no NH band.

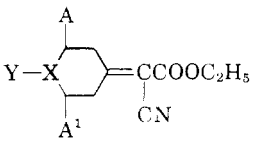
Cyclohexane-α,α'-dimethyl-1,1-diacetic Acid.—Hydrolysis of the trimethyl imide (22 g.) was accomplished by dissolving in 96 g. of concd. sulfuric acid, allowing to stand overnight, adding 96 g. of water, and refluxing for 8 hr. During the reflux period, the mixture was shaken at intervals. After cooling, 500 ml. of water was added and the crude product was filtered. The acid was dissolved in potassium bicarbonate solution, treated with charcoal, filtered, and the solution acidified with hydrochloric acid. After filtering and drying, the product (7 g.) melted at 143–144°. When recrystallized from a 50% methanol–water mixture, it melted at 143–145°.

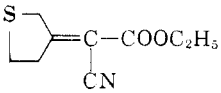
Cyclohexane-α,α'-dimethyl-1,1-diacetic Acid Anhydride.—Six g. of the above acid was refluxed for 3 hr. with 20 ml. of acetic anhydride. The excess of acetic anhydride was removed under reduced pressure and the residue was distilled under vacuum. The product was collected at 106–107° (0.5 mm.) as an oil which crystallized in the receiver. It melted at 60–61° and recrystallization from benzene–hexane did not change the melting point.

N-Dimethylaminopropyl-1,5-dimethyl-3-azaspiro[5:5]undecane

TABLE XVII

ALKYLIDENE CYANOACETIC ESTERS



	Y	X	A	A¹	Formula	B.p., °C. (mm.)	Analysis, %: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1.	$(CH_3)_3C$	CH	H	H	$C_{15}H_{23}NO_2$	119–121[b] (0.25)	72.25	72.53	9.30	9.29	5.62	5.92
2.	CH_3	CH	H	H	$C_{12}H_{17}NO_2$	109–112 (0.5)	69.54	69.41	8.27	8.35	6.76	6.86
3.		CH_2	CH_3	H	$C_{12}H_{17}NO_2$	85–90 (0.05)	69.54	69.37	8.27	8.60	6.76	6.88
4.		O	H	H	$C_{10}H_{13}NO_3$	95–100 (0.2[c])	61.52	61.58	6.71	6.68	7.18	7.14
5.		O	CH_3	CH_3	$C_{12}H_{17}NO_3$	104–104.5[d]	64.55	64.58	7.68	7.86	6.28	6.38
6.		O	CH_3	C_6H_5[a]	$C_{17}H_{19}NO_3$	160–165 (0.3)	71.56	71.47	6.71	6.84	4.91	5.03
7.		S	H	H	$C_{10}H_{13}NO_2S$	111–115[e] (0.03)	56.85	56.83	6.20	6.23	6.63	6.65
8.					$C_9H_{11}NO_2S$	106–111 (0.35)	54.80	54.94	5.62	5.70	7.10	7.01

[a] Phenyl. [b] M.p. 41–42°. [c] V. Prelog, D. Kohlback, E. Cerkovnikov, E. Rezek, and M. Piantanida, *Ann.*, **532**, 69 (1937). [d] M.p. [e] Calcd.: S, 15.18. Found: S, 15.14.

TABLE XVIII

CLINICAL OBSERVATIONS WITH N-DIMETHYLAMINOPROPYL-9-*t*-BUTYL-3-AZASPIRO[5:5]UNDECANE[a]

Patient	Diagnosis	Interval of treatment, months	Results
D.A. W.F.—57	Mammary carcinoma, osseous and pulmonary metastasis	15	Regression of tumor and symptom with marked clinical benefit for 10 months.
B.D. W.M.—38	Recurrent colonic carcinoma. Peritoneal and hepatic metastasis	4	3-Month remission of symptoms only.
M.C. W.F.—61	Nasopharyngeal carcinoma. Lymph node metastasis	2	Temporary benefit only.
K.A. W.M.—61	Colonic carcinoma with hepatic and abdominal wall metastasis	10	Regression of symptoms 10 months.
H.F. W.M.—57	Osteogenic sarcoma with skin metastasis	5	No appreciable benefit. Discontinued treatment.
K.F. W.F.—46	Mammary carcinoma. Supraclavicular metastasis.	13	Regression of tumor for 24 months.
G.McG. W.F.—22	Grade I fibrosarcoma. Desmofibromatosis	24	Moderate regression tumor. Relief symptoms 2.5 years.
F.R. W.F.—59	Recurrent gastric carcinoma	4	Regression tumor masses for 3 months. Intestinal obstruction relieved.
C.C. W.F.—47	Mammary carcinoma with osseous metastasis	14	Regression symptoms for 18 months.
O.H. W.M.—66	Bronchogenic carcinoma. Recurrent	2	Remission of symptoms. Tumor stationary 1 month.
G.E. W.F.—52	Myosarcoma of stomach with intra-abdominal extension with obstruction	5	Formerly bedridden. Now up and around after 4 months.
O.W. W.F.—36	Uterine adenocarcinoma with frozen pelvis. Vascular obstruction of iliac and femoral vessels	4	Vascular obstruction relieved. Marked symptomatic improvement.
P.R. W.F.—44	Grade IV carcinoma bladder with invasion of vagina and ulceration of abdominal wall	5	Terminal status at onset of therapy. Now ambulatory 4 months.
S.A. W.F.—49	Reticulum cell sarcoma of lymph nodes, generalized	8	Regression of masses with a 6-month remission. Gradual return symptoms thereafter.
O.S. W.F.—66	Colonic carcinoma with hepatic metastasis	9	Regression of symptoms for 7 months.
A.S. W.F.—38	Reticulum cell sarcoma with involvement lymph glands	15	Marked regression of tumor masses and disappearance of pleural effusion for 12 months.
B.A. W.F.—46	Mammary carcinoma with bilateral pulmonary metastasis	4	Marked relief of symptoms and pain. Lymphedema and pleural effusion disappeared.
M.R. W.M.—55	Carcinoma of the bowel	2	Symptomatic relief of pain. No regression of tumor.

[a] The drug may be given I.V., I.M., or by perfusion and is tolerated.

Dihydrochloride.—To 4.2 g. (0.02 mole) of the previously mentioned anhydride was added 2.5 g. (excess) of dimethylaminopropylamine and the mixture was heated to 180° for 1 hr. It was allowed to cool and added in ether to a solution of 2 g. of lithium aluminum hydride in 200 ml. of anhydrous ether. After stirring for 2 hr., the solution was decomposed with water, filtered, dried over sodium sulfate, and stripped. The resultant oil was dissolved in absolute alcohol and an ethanol solution of hydrogen chloride was added. The product was precipitated with ether and after filtering and drying, it melted at 300–302°. One recrystallization from ethanol–ether raised the melting point to 304–305° which was unchanged on further recrystallization.

TABLE XIX

CYCLOALKANE-1-CARBOXY-1-ACETIC ACIDS AND ANHYDRIDES

	Y	X	A	A'	Formula	M.p., °C.	Analysis, % Acids — Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	B.p., °C. (mm.)	M.p., °C.	Anhydrides — Analysis, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1.	$(CH_3)_2C$	CH	H	H	$C_{13}H_{22}O_4$	191–192	64.44	64.50	9.15	9.34	138–142 (0.25)	112–113	69.61	69.52	8.99	9.20
2.	CH_3	CH	H	H	$C_{10}H_{16}O_4$	161	59.98	60.10	8.05	7.98	85–90 (0.2)		65.91	65.85	7.74	7.90
3.		CH_2	CH_3	H	$C_{10}H_{16}O_4$	160	59.98	59.63	8.05	8.06	85–87 (0.1)		65.91	65.72	7.74	7.68
4.		O	H	H	$C_8H_{12}O_5$	150–151	51.06	50.96	6.43	6.37		105–106.5	56.41	56.35	5.92	6.00
5.		O	CH_3	CH_3	$C_{10}H_{16}O_5$	196–197	55.55	55.67	7.46	7.76	98–105 (0.02)	68–70	60.59	60.78	7.12	7.39
6.		O	CH_3	C_6H_5[a]	$C_{15}H_{18}O_5$		64.73	64.58	6.52	6.63	160–165 (0.4)		69.21	68.98	6.20	6.15
7.		S	H	H	$C_8H_{12}O_4S$	132–133.5	47.04	47.10	5.92	6.01	142–147 (0.05)	94–95	51.60	51.48	5.41	5.52
8.		S	CH_2COOH COOH		$C_7H_{10}O_4S$	157–158	44.20	44.15	5.30	5.22	124–130 (0.25)	79–80	48.82	48.95	4.68	4.52

[a] Phenyl.

Anal. Calcd. for $C_{17}H_{36}Cl_2N_2$: Cl, 20.89. Found: Cl, 20.97.

Ethyl α-Cyano-α-(3-thiacyclopentylidene)acetate.—Tetrahydrothiophene-3-one (60 g.) was mixed with 1 molar equiv. (67 g.) of ethyl cyanoacetate and 1 ml. of piperidine was added. The mixture was stoppered tightly and allowed to stand 1 week at room temperature. The reaction mixture was poured into 1 l. of half-saturated aqueous sodium chloride containing 1 ml. of concd. hydrochloric acid. This was mixed thoroughly in a separatory funnel and extracted 3 times with 300-ml. portions of ether. The ether extracts were dried over sodium sulfate, the ether was stripped, and the residue was fractionally distilled under vacuum yielding 54 g. of product, b.p. 106–111° (0.35 mm.); m.p. from acetone–water 57.5–58.5°.

3-Thiacyclopentane-1-carboxy-1-acetic Acid.—Fifty-four grams of the above ester was placed in a 500-ml. flask, dissolved in 250 ml. of alcohol, and a solution of 40 g. of potassium cyanide in 85 ml. of water added. The mixture was permitted to stand at room temperature for 72 hr. and was stripped of all solvents under reduced pressure until a dried powder remained. Concd. hydrochloric acid (200 ml.) was added to the powder through a long condenser and the mixture was refluxed for 24 hr., cooled in the ice box, and filtered, yielding 45 g. of crude acid with a brownish tint. This was redissolved in a minimum of boiling water, treated with decolorizing charcoal, filtered, and cooled. The product was obtained as long white needles (37.5 g.), m.p. 156–157°. When the filtrate was combined with the hydrochloric acid filtrate mother liquor and extracted in a continuous ether extractor for 24 hr., another 5 g. of acid was obtained. On recrystallization from acetone–ligroin, the pure acid melted at 157–158°.

3-Thiacyclopentane-1-carboxy-1-acetic Acid Anhydride.—Refluxing 42 g. of the acid above with 200 ml. of acetic anhydride for 2 hr., stripping off the acetic anhydride at the water pump, and distillation of the residue under vacuum yielded 35 g. of material, b.p. 124–130° (0.25 mm.), m.p. 79–80°.

Ethyl α-Cyano-α-(4-thiacyclohexylidene)acetate.—To 30 g. (0.26 mole) of penthianone was added 29.4 g. (0.26 mole) of ethyl cyanoacetate and 0.3 ml. of piperidine and the mixture was heated to 100°. After 3 days of standing and heating to 100° once each day, the reaction mixture was poured into 250 ml. of water containing 2 ml. of hydrochloric acid. The resulting oil was extracted with ether and the ethereal extract was dried, stripped, and the residue was distilled. The product boiled at 111–115° (0.03 mm.) and weighed 39.2 g.

4-Thiacyclohexane-1-carboxy-1-acetic Acid.—To 38.2 g. of the above ester in 450 ml. of alcohol was added a solution of 13 g. of potassium cyanide in a small amount of water. After standing 3 days, the solvent was removed under reduced pressure and the residue was refluxed with 100 ml. concd. hydrochloric acid for 24 hr. On cooling, the product crystallized and was filtered (32 g., 87%). It melted at 130–132° and one recrystallization from water raised the melting point to 132–133.5°.

4-Thiacyclohexane-1-carboxy-1-acetic Anhydride.—From 30 g. of the above acid using acetic anhydride followed by distillation in the usual way, there was obtained 22 g. of anhydride 80.4% boiling at 142–147° (50 μ). The anhydride solidified on standing and recrystallization from ethyl acetate–ligroin gave material melting at 94–95°.

Ethyl α-Cyano-α-(3,5-dimethyl-4-oxacyclohexylidene)acetate.—2,6-Dimethyltetrahydro-γ-pyrone (29 g.), 1 molar equiv. of ethyl cyanoacetate, and 0.1 ml. of piperidine were heated to boiling and stoppered. Each day for 5 days, the procedure of heating and adding 0.1 ml. of piperidine was repeated. The ester crystallized in large blocks which were filtered off and washed with petroleum ether. It melted at 103–105° and on recrystallization from acetone–water melted at 104–104.5° (yield, 31 g.).

3,5-Dimethyl-4-oxacyclohexane-1-carboxy-1-acetic Acid.—Thirty-one g. of the ester from above dissolved in 450 ml. of alcohol (this ester was rather insoluble in alcohol) was treated with 10 g. of potassium cyanide in 20 ml. of water. After 5 days, the mixture was stripped under reduced pressure until a dry powder remained. Hydrolysis of the cyanide addition product with 350 ml. of concd. hydrochloric acid for 24 hr., stripping to dryness, and repeated extraction of the residue with boiling ethyl acetate yielded 21 g. of the acid (m.p. 196–197°). Recrystallization from ethyl acetate resulted in a product, m.p. 196–197°.

3,5-Dimethyl-4-oxacyclohexane-1-carboxy-1-acetic Acid Anhydride.—Conversion of the acid to the anhydride in the usual manner using acetic anhydride yielded 16 g. of anhydride, b.p. 98–105° (0.02 mm.), m.p. 68–70°.

1,5-Dicyano-8,10-dimethyl-9-oxa-3-azaspiro[5.5]undecane-2,4-dione.—Condensation of 66 g. of 2,6-dimethyltetrahydro-γ-pyrone with 2 molar equiv. (117 g.) of ethyl cyanoacetate in an excess of saturated anhydrous ammonia in absolute alcohol for 5 days at 5° yielded 87 g. of the ammonium salt of the dicyanoimide. This was dissolved in a minimum of boiling water and acidified with concd. hydrochloric acid. Cooling overnight in the refrigerator and filtering yielded 63 g. of the dicyanoimide (m.p. 230–231°). Recrystallization from water resulted in a product, m.p. 231–232°.

3,5-Dimethyl-4-oxacyclohexane-1,1-diacetic Acid.—Hydrolysis of the dicyanoimide with 40–60% sulfuric acid resulted in poor yields of the desired acid due to destruction of the pyrone ring by the sulfuric acid. The desired acid was obtained by stepwise hydrolysis as follows: the imide was boiled for several hours with a 2% aqueous solution of sodium hydroxide until ammonia ceased to be evolved. This procedure ruptured the imide ring. The resultant solution was concentrated under reduced pressure and the hydrolysis completed either by (A) boiling with 15% NaOH or (B) concd. hydrochloric acid. The acid was extracted by continuous ether extraction overnight. This yielded the tetracarboxylic acid mixed with the desired dicarboxylic acid. The mixture of acids was heated slowly until effervescence of carbon dioxide ceased (decarboxylation of the tetracarboxylic acid), cooled, and recrystallized from water after treating with decolorizing charcoal. The crude acid melted at 137–141° by either alternative hydrolysis procedure. On recrystallization from acetone–petroleum ether, it melted at 155–156°.

3,5-Dimethyl-4-oxacyclohexane-1,1-diacetic Acid Anhydride.—The anhydride was formed by treating the acid with excess acetic anhydride and vacuum distilling the residue. The resultant anhydride boiled at 132–137° (0.04 mm.) and melted at 110–111°.

1,5-Dicyano-8-thia-3-azaspiro[5:4]decane-2,4-dione.—At 0°, a mixture of 30 g. of 3-ketotetrahydrothiophene and 68 g. of ethyl cyanoacetate was added to 200 ml. of alcohol which had previously been saturated with ammonia at 0°. The reaction vessel with stopper wired down was allowed to stand for 1 week and filtered. After washing the product with a little alcohol–ether mixture, the ammonium salt was dissolved in a minimum amount of water and acidified with hydrochloric acid. The product was filtered, dried, and recrystallized from ethanol water. It weighed 20 g. and melted at 221–222°. When attempts were made to hydrolyze this product to the diacetic acid with sulfuric acid, extensive decomposition occurred.

1,5-Dicyano-9-thia-3-azaspiro[5:5]undecane-2,4-dione.—Fifty g. of penthianone and 98 g. of ethyl cyanoacetate were mixed, cooled, and added to a solution of 400 ml. of alcohol saturated with ammonia at 0°. The stopper was wired down. After standing in a cold room for 1 week, the mixture was filtered and washed with an alcohol–ether mixture. When almost dry, the precipitate was dissolved in a minimum amount of hot water and acidified with hydrochloric acid. The solution was cooled and the product filtered off. It weighed 32 g. and on recrystallization from alcohol–water melted at 208–210°.

4-Thiacyclohexane-1,1-diacetic Acid.—The above dicyanoimide (30 g.) was refluxed with 200 ml. of concd. hydrochloric acid for 24 hr. There was a large amount of material which did not go into solution. The mixture was filtered hot and 16 g. of material was collected. This was only partly hydrolyzed material and is described below. The filtrate was cooled and 10.5 g. of off-white crystals were collected which melted at 172–173°. Recrystallization from water raised the melting point to 174–175°.

The 16 g. of insoluble partly hydrolyzed material obtained above did not melt at 360° and was insoluble in ether, alcohol, water, and most of the usual organic solvents. It did dissolve in sodium hydroxide. In conjunction with infrared spectra, it is believed that this material is the internal imide of 9-thia-3-azaspiro[5:5]undecane-2,4-dione formed at positions 1 and 5 from 9-thia-3-azaspiro[5:5]undecane-1-carboxy-5-carbanido-2,4-dione.

Anal. Calcd. for $C_{11}H_{12}N_2O_4S$: C, 49.23; H, 4.51; N, 10.44; S, 11.95. Found: C, 49.37; H, 4.60; N, 10.61; S, 11.61.

Cyclopropane Methonium Compounds[1]

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In a study of the effect of limiting the flexibility of the chains of methonium compounds on the pharmacological actions of certain stereoisomers, analogs of hexamethonium and succinylcholine carrying a *cis* or *trans* oriented cyclopropane ring in the center of the chain were synthesized. The geometric isomers of bis(trimethylammoniumethyl)cyclopropane-1,2-dicarboxylate and of the homologous cyclopropane-1,2-diacetate ester diiodides caused predominantly neuromuscular block and resembled succinylcholine. The geometric isomers of 1,2-di-(β-trimethylammoniumethyl)cyclopropane diiodide exerted primarily ganglionic blockade of the hexamethonium type. The *trans* isomer was the more potent in each case.

The methonium compounds have provided relatively simple examples for the study of quantitative and qualitative differences in biological response depending on chain length and intramolecular distances between onium centers.[2] On the whole, linear chains of 5 to 7 carbon atoms [or their equivalent such as —O—, —N(CH$_3$)—] favor ganglionic blocking activity, while 9–11 chain atoms produce primarily agents which depolarize the cholinergic end plate. Longer alkyl chains lead to surface active agents although a bulky aromatic substituent in the middle of the chain may under some circumstances increase curaremimetic activity up to 13 chain atoms; at this chain length increases of the blood pressure may be observed.[3] However, ganglionic blocking is optimal also when a methonium ion is separated from another ammonium group by only two carbon atoms, provided that this other ammonium nitrogen is shielded by the bulk of surrounding structures.[4] The inactivity of *p*-(CH$_3$)$_3$N$^+$C$_6$H$_4$CH$_2$N$^+$(CH$_3$)$_3$ and similar rigid structures in

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