(DMF). Compounds **15** and **19** were prepared by the same method.

3-Cyanomethylimidazo[1,2-*a*]pyridine (6). Method D.—The methiodide of the 3-dimethylaminomethylimidazo[1,2-*a*]pyridine[4] (83.7 g, 0.26 mole) was dissolved in 500 ml of EtOH, previously dried with $NaBH_4$, NaCN (38.9 g, 0.8 mole) was added, and the mixture refluxed for 16 hr. After filtering, the EtOH was removed under vacuum and the residue was taken up in H_2O (250 ml) and extracted (CH_2Cl_2, 1500 ml). The solvent was decolorized and evaporated. The residue was crystallized (C_6H_6) collecting a first crop (11 g). The filtrate was percolated through alumina and concentrated to about one-third volume. A second crop was collected (10 g), yield 51%. Compounds **7–9** were synthesized by the same procedure.

2-Methyl-3-carboxamidomethylimidazo[1,2-*a*]pyridine (18). Method E.—The 2-methyl-3-dimethylaminomethylimidazo-[1,2-*a*]pyridine methiodide[4] (100 g, 0.3 mole) was dissolved in 400 ml of H_2O, treated with 44.6 g (0.9 mole) of NaCN, and refluxed for 3 hr. After cooling, the solution was extracted (CH_2Cl_2) and the solvent was discarded. After 16 hr at 5°, a crystalline solid was filtered and recrystallized from H_2O giving 41 g (73%) of **18**. Compounds **17**, **19**, and **20** were obtained by the same procedure.

(3-Imidazo[1,2-*a*]pyridine)acetic Acid (25). Method E.—A mixture of 9.5 g (0.03 mole) of the 3-dimethylaminomethylimidazo[1,2-*a*]pyridine methiodide and 4.42 g (0.09 mole) of NaCN in 96 ml of H_2O was refluxed for 3 hr; the $N(CH_3)_3$ and NH_3 gas were collected in a 3% solution of H_3BO_3 and titrated with 1 *N* H_2SO_4. The theoretical amount of 60 ml was used. The solution obtained was evaporated under vacuum and the residue was washed (Me_2CO, EtOAc). The solid (6.6 g) was dissolved in 25 ml of H_2O and the pH was adjusted to 6.7 with AcOH. Compound **25** was filtered and recrystallized from 99% EtOH (2.8 g, 53%).

3-Carboxamidomethylimidazo[1,2-*a*]pyridine (16). Method F.—An intimate mixture of 3 g (0.017 mole) of (3-imidazo-[1,2-*a*]pyridine)acetic acid (**25**) and 3 g of urea was melted and heated at 190–195° for 3 hr. After cooling, the residue was washed (5% $NaHCO_3$, cold Me_2CO) and recrystallized (MeOH) (1.5 g, 51.8%).

(2-Methyl-3-imidazo[1,2-*a*]pyridine)acetic Acid (27). Method G.—A solution of 6 g (0.032 mole) of the amide **18** and 15 g of KOH in 30 ml of H_2O and 120 ml of 95% EtOH was refluxed under N_2 for 2 hr. The NH_3 gas was collected in a 5% solution of H_3BO_3 and titrated with 1 *N* H_2SO_4. The solution was evaporated and the residue was dissolved in 40 ml of H_2O and decolorized. The solution was adjusted to pH 7 with AcOH and the precipitated solid was collected, yield 4 g (61%). The above procedure was used to synthesize the carboxylic acids **21**, **22**, and **31** starting from the corresponding amides, and **23–25**, and **30** starting from the nitriles. The acid **26**, which was very soluble in H_2O, could be obtained by hydrolyzing the corresponding nitrile, by percolating the alkaline solution over Amberlite IRC 50 (CO_2H form), and by evaporating the eluate to dryness.

The 2-(4-chlorophenyl)-3-carboxyimidazo[1,2-*a*]pyridine could not be prepared because both alkaline and acidic hydrolysis of the nitrile **4** or of the amide **14** led to extensive decarboxylation; 2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine[14] was the only compound isolated.

2,7-Dimethyl-3-carboxymethylimidazo[1,2-*a*]pyridine (29). Method H.—A solution of 2-amino-4-methylpyridine (21.6 g, 0.2 mole) and methyl 3-bromolevulinate (20.9 g, 0.1 mole) in 99% EtOH (80 ml) was stirred at 60° for 3 hr. The solvent was removed *in vacuo* and the residue, dissolved in H_2O, was alkalized with NaOH and extracted ($CHCl_3$). The aqueous layer was brought to pH 6.7 with AcOH and distilled *in vacuo* until dry. The residue was triturated with H_2O (15 ml) and the solid obtained was filtered and washed with ice–water. The acid **29** was recrystallized from 85% EtOH (36 ml) as a white, hygroscopic crystalline solid (6 g). Compounds **27** and **28** were obtained by the same procedure.

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Spirans. XV. Spirans Derived from 3-Trifluoromethylcyclohexanone[1,2]

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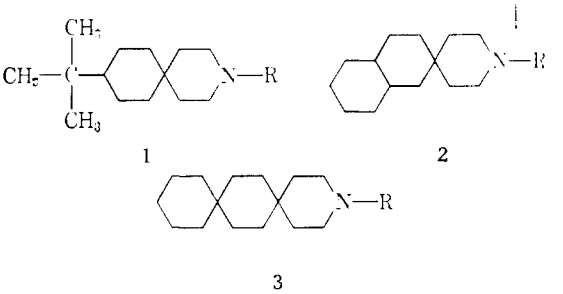
Various spiro[5.4]decane and spiro[5.5]undecane compounds containing a trifluoromethyl substitution in the 7 or 8 position have been synthesized. When evaluated biologically, *N*-(3-dimethylaminopropyl)-8-trifluoromethyl-3-azaspiro[5.5]undecane showed the best activity and is potentially an interesting anticancer compound.

Molecular modification of a parent compound has long been a tool in the design of safer and more effective synthetic analogs. In numerous cases, the trifluoromethyl group has led to compounds with a more favorable ratio of primary activity to side effects. With this as a basic corollary, we have now evaluated the effect on potency and other reactions of the trifluoromethyl group when introduced in position 8 or 3-azaspiro[5.5]undecane and position 7 of 2-azaspiro[5.4]decane (Table I).

We have been interested in the cytotoxicity of 3-azaspiro[5.5]undecanes and have previously reported on the activity of 9-butyl (**1**),[3] 8,9-cyclotetramethylene (**2**),[4] and 9,9-cyclopentamethylene (**3**)[1,5] derivatives.



1 2 3

All of these compounds have an inhibitory activity in the range of 1 μg/ml or less when tested on the growth

(1) Part XIV: L. M. Rice and K. R. Scott, *J. Med. Chem.*, **11**, 378 (1968).

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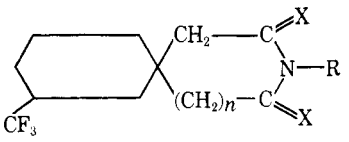
TABLE I

3-TRIFLUOROMETHYLSPIRAN DERIVATIVES[a]



n	X	R	Bp (mm) or mp, °C	Formula	Method[b]
0	O	H	110–112	$C_{10}H_{12}F_3NO_2$	A
0	H_2	H	40–42 (0.07)	$C_{10}H_{16}F_3N$[c–e]	B
0	O	CH_3	130–131	$C_{11}H_{14}F_3NO_2$	A
0	H_2	CH_3	60–64 (0.5)	$C_{11}H_{18}F_3N$[f,g]	B
0	O	$CH_2CH{=}CH_2$	95–98 (0.13)	$C_{13}H_{16}F_3NO_2$	C
0	H_2	$CH_2CH{=}CH_2$	55–58 (0.17)	$C_{13}H_{20}F_3N$	B
0	O	C_8H_{15}[h]	160–164 (0.02)	$C_{18}H_{26}F_3NO_2$	C
0	H_2	C_8H_{15}	110–114 (0.12)	$C_{18}H_{30}F_3N$[i,j]	B
0	O	C_7H_6F[k]	Glass	$C_{17}H_{17}F_4NO_2$	A
0	H_2	C_7H_6F	109–112 (0.08)	$C_{17}H_{21}F_4N$[l]	B
0	O	$C_{10}H_{13}O_2$[m]	Glass	$C_{20}H_{25}F_3NO_4$	A
0	H_2	$C_{10}H_{13}O_2$	145–150 (0.10)	$C_{20}H_{29}F_3NO_2$[n,o]	B
0	O	$C_7H_{14}NO$[p]	170–180 (0.13)	$C_{17}H_{25}F_3N_2O_3$[q]	C
0	H_2	$C_7H_{14}NO$	120–125 (0.08)	$C_{17}H_{29}F_3N_2O$[r]	B
0	O	$N(CH_3)_2$	67.5–69	$C_{12}H_{17}F_3N_2O_2$	A
0	H_2	$N(CH_3)_2$	49–51 (0.05)	$C_{12}H_{21}F_3N_2$	B
1	O	H	184–185	$C_{11}H_{14}F_3NO_2$	A
1	H_2	H	124–125 (24.0)	$C_{11}H_{18}F_3N$[s]	B
1	O	$N(CH_3)_2$	Glass	$C_{13}H_{19}F_3N_2O_2$	A
1	H_2	$N(CH_3)_2$	73–75 (0.08)	$C_{13}H_{23}F_3N_2$[t]	B
1	O	$C_5H_{12}N$[u]	140–145 (0.12)	$C_{16}H_{25}F_3N_2O_2$[v]	C
1	H_2	$C_5H_{12}N$	92–100 (0.15)	$C_{16}H_{29}F_3N_2$[v]	B
1	H_2	$C_{10}H_{10}FO$[w]	239–240	$C_{21}H_{28}F_4ClNO$[x]	

[a] Analytical results were within ±0.4% for C, H, and N for all compounds listed. [b] See Experimental Section. [c] Hydrochloride mp 103–105°. *Anal.* ($C_{10}H_{17}ClF_3N$) Cl, N. [d] Picrate mp 184–185°. *Anal.* ($C_{16}H_{19}F_3N_4O_7$) N. [e] Phenylthiourea mp 172–173°. *Anal.* ($C_{17}H_{21}F_3N_2S$) N. [f] Methiodide mp 267–268°. *Anal.* ($C_{12}H_{21}F_3IN$) I. [g] Hydrochloride mp 215–217°. *Anal.* ($C_{11}H_{19}ClF_3N$) Cl. [h] Cyclooctyl. [i] Methiodide mp 247–248°. *Anal.* ($C_{19}H_{33}F_3IN$) I. [j] Hydrochloride mp 148–150°. *Anal.* ($C_{18}H_{31}ClF_3N$) Cl. [k] *p*-Fluorobenzyl. [l] Hydrochloride mp 204–206°. *Anal.* ($C_{17}H_{22}ClF_4N$) Cl. [m] Homoveratryl. [n] Hydrochloride mp 174–175°. *Anal.* ($C_{20}H_{30}ClF_3NO_2$) Cl. [o] Methiodide mp 197–199°. *Anal.* ($C_{21}H_{32}F_3INO_2$) I. [p] Morpholinopropyl. [q] Methiodide mp 168–170°. *Anal.* ($C_{18}H_{28}F_3IN_2O_2$) I. [r] Dimethiodide mp 231–233°. *Anal.* ($C_{19}H_{35}F_3I_2N_2O$) I. [s] Hydrochloride mp 242–243°. *Anal.* ($C_{11}H_{19}ClF_3N$) Cl. [t] Hydrochloride mp 197–198°. *Anal.* ($C_{13}H_{24}ClF_3N_2$) Cl, N. [u] 3-Dimethylaminopropyl. [v] Analyzed for F. [w] 3-(*p*-Fluorobenzoyl)propyl (see Experimental Section). [x] Analyzed for Cl.

of KB tissue culture cells. In addition, testing was also done on human mammary cancer cells with similar results. It is of interest that the molecular weight of each of the three groups, *t*-butyl (**57**), tetramethylene (**54**), and pentamethylene (**70**) lie between 54 and 70 while the molecular weight of the trifluoromethyl group is 69. Clearly, the molecular weight alone is not the primary factor in the selective activity of these agents. The trifluoromethyl moiety is the most electronegative and any increase or decrease in activity of these reported compounds should be attributable to this factor.

The starting material in our synthesis was 3-trifluoromethylcyclohexanone (I), obtained by the catalytic hydrogenation of *m*-trifluoromethylphenol followed by oxidation.[6] This ketone was subjected to the various reactions as shown in Chart I. The 3-azaspiro[5.5]undecane derivative II was prepared by the condensation of ketone I with ethyl cyanoacetate and saturated alcoholic NH_3 at 0°. It is important that a minimum volume of EtOH be used in this case due to the solubility of the Guareschi salt in this solvent. Hydrolysis of the dicyanoimide with 70% H_2SO_4 yielded acid III which was converted into the anhydride IV. Reaction of IV and IX with a variety of amines yielded the amic acids which were cyclized smoothly at 180–200° to form the imides V and X, respectively. When the imides were solids, purification by recrystallization was accomplished; when they occurred as oils, distillation was the means of achieving analytical purity. $LiAlH_4$ reduction of the imides to the corresponding bases proceeded. Data on the imides, amines, and their derivatives are listed in Table I.

The preparation of acid VIII followed the reaction of ketone I with ethyl cyanoacetate, using a modified Cope[7] procedure, producing the cyanoalkylidene ester VII. Addition of NaCN across the double bond, followed by hydrolysis with concentrated HCl, produced acid VIII. Acid VIII was converted with Ac_2O to IX.

Due to the excellent analgetic and analeptic properties of 3-aminospiro[5.5]undecane,[8] it was of interest to prepare the corresponding trifluoromethyl analog XIX. This was performed as follows. Acid III was converted into its ester and reduced to the glycol XII. Dehydration of XII with 48% HBr gave the corresponding spirotetrahydropyran XIII, which with 48% HBr and H_2SO_4 produced the dibromide XIV. Conversion of XIV to the dinitrile XV with alcoholic KCN and hydrolysis with concentrated HCl produced the diacid XVI in excellent yield. Pyrolysis of the acid XVI in the presence of $Ba(OH)_2$ at 290–300° yielded ketone XVII which was readily converted into the oxime XVIII and reduced to the desired amine XIX in excellent yield.

Because of the potent neuroleptic properties of 3-(*p*-fluorobenzoyl)propyl-3-azaspiro[5.5]undecane,[9] it was desirable to prepare the corresponding analog with an 8-trifluoromethyl substitution. This was readily accomplished by the reaction of V (R′ = H) with 4-chloro-*p*-fluorobutyrophenone in the presence of a trace amount of KI. The butyrophenone derivative had an LD_{50} of 100 mg/kg ip and produced a decreased motor activity and antimorphine activity at 3 mg/kg. It was somewhat more potent than chlorpromazine in producing sedation.[9] In addition, it had a faster onset of action than the corresponding unsubstituted compound.

The 3-aminospiro[5.5]undecane derivative XIX had about the same order of activity as the 8-unsubstituted compound when tested for analgetic and analeptic activity using the methods previously outlined.[8] All of the compounds when tested in either KB or mammary cancer cell cultures displayed no appreciable activity except for compounds of type VI and XI where R′ was the dialkylaminoalkyl group. One of these compounds, VI [R′ = $(CH_2)_3N(CH_3)_2$], has been studied in some detail. It is active at 1 μg/ml in both of the above cell cultures and compared favorably with compounds of the type **1**, **2**, and **3**. It has an LD_{50} of 200 mg/kg ip in rats and a 3-month chronic toxicity screen in rats at either 5 or 10 mg/kg ip showed no de-

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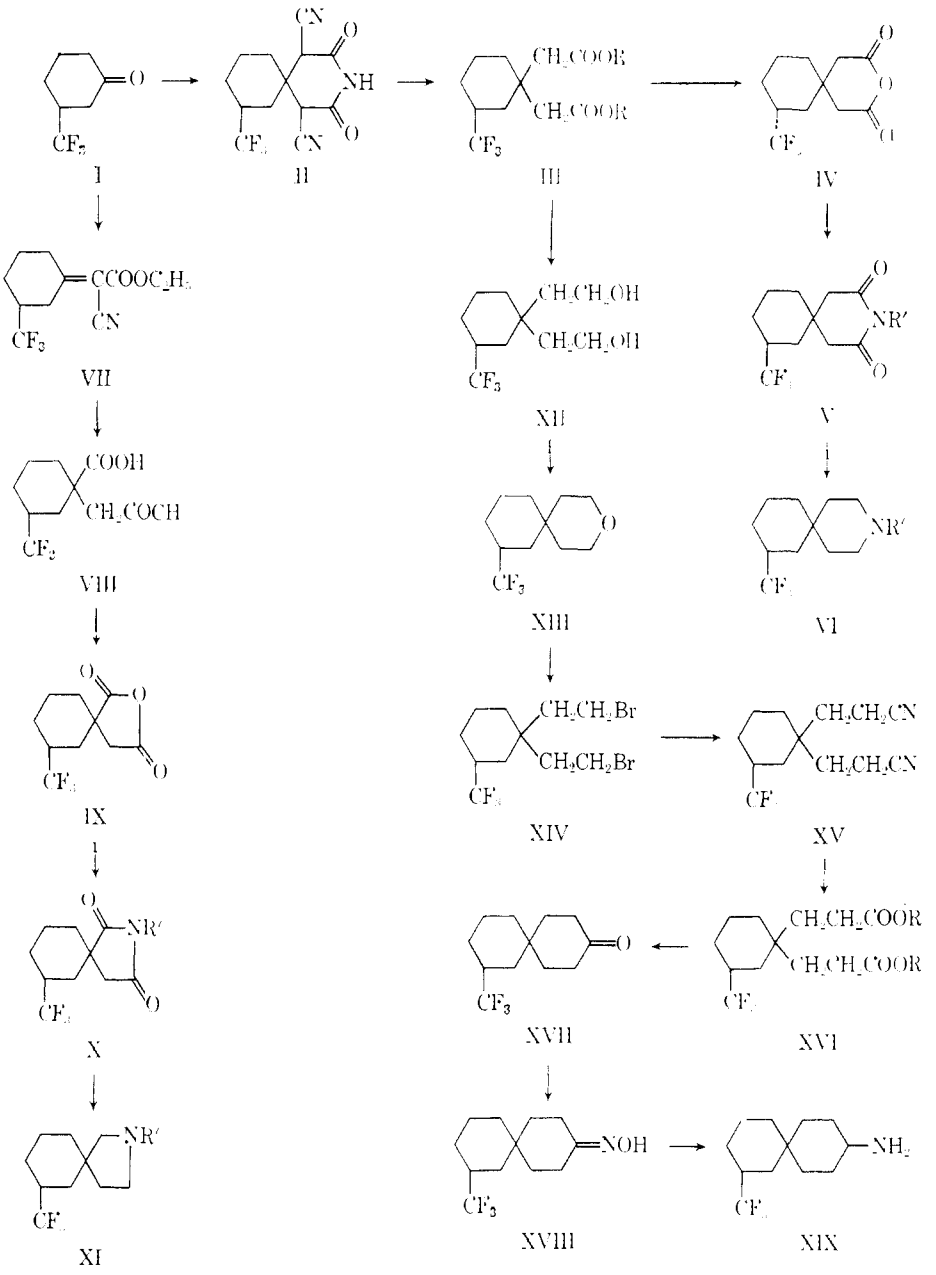
(7) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *ibid.*, **63**, 3452 (1941).

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

(9) C. H. Grogan, C. F. Geschickter, M. E. Freed, and L. M. Rice, *ibid.*, **8**, 62 (1965).

CHART I



R = H, C_2H_5; R′ = H or aliphatic amine

tectable pathology. All animals maintained weight and growth. In addition, a 50 mg/kg ip daily dosage for 5 days showed no reaction. The compound is well tolerated in patients and has had an inhibitory effect for over 1 year in patients with advanced stages of cancer of the breast and prostate.

Experimental Section

All melting points (Thomas–Hoover capillary-type apparatus) are corrected. Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. The infrared spectra of all compounds corresponded with assigned structures. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

Trifluoromethylcyclohexanone (I).—*m*-Trifluoromethylphenol was distilled and 131 g (0.81 mole) was dissolved in 200 ml of EtOH and hydrogenated (1 g of Pt catalyst, 160°, 63.27 kg/cm²) for 6 hr. The reaction mixture, consisting mainly of unreacted starting material, 3-trifluoromethylcyclohexanol, and 3-trifluoromethylcyclohexanone[10] was dissolved in 600 ml of Et_2O and was washed several times with 100-ml portions of 10% NaOH. After drying (Na_2SO_4) and removing all organic solvents, the mixture was dissolved in Et_2O and oxidized by the H_2CrO_4 procedure of Brown.[6] The product (48 g, 28%) was obtained by distillation, bp 175–177° (46°, 4 mm). A glpc analysis of the distillate on the 305-cm UCON column (column temperature, 225°; helium flow, 100 ml/min) showed it to be greater than 97% pure. *Anal.* ($C_7H_9F_3O$) C, H, F.

The **2,4-dinitrophenylhydrazone** was prepared in the usual manner, mp 167–168° (EtOH). *Anal.* ($C_{13}H_{13}F_3N_4O_4$) C, H, F, N. The **thiosemicarbazone**, mp 135–137° (MeOH–H_2O). *Anal.* ($C_8H_{12}F_3N_3S$) C, H, F, N. The **oxime**, mp 52–53° (ligroin). *Anal.* ($C_7H_{10}F_3NO$) C, H, F, N.

1,5-Dicyano-8-trifluoromethyl-3-azaspiro[5.5]undecane-2,4-dione (II).—Compound I (160 g, 0.96 mole) and 226 g (2.0 moles) of ethyl cyanoacetate were mixed and cooled to 0°. EtOH (500 ml) saturated with NH_3 at 0° was added and the mixture was stoppered and stored at 0–5° for 1 week. At the end of this period the precipitated NH_4^+ salt was filtered and washed

(10) Trace amounts of 3-methylcyclohexanone, toluene, and difluorotoluene were also obtained but were not investigated further.

with Et_2O. The filtrate was diluted with 1 l. of dry Et_2O and permitted to stand overnight at 0–5°. An additional crop was obtained, which was filtered, washed, and combined with the original (total, 145 g of dried product). The ammonium salt was dissolved in 1.5 l. of boiling H_2O and acidified with 500 ml of concentrated HCl. Compound II, which precipitated, was filtered, washed (H_2O), and dried (132 g, 46%). Recrystallization from EtOH–H_2O, mp 245–246°. *Anal.* ($C_{13}H_{12}F_3N_3O_2$) C, H, F, N.

3-Trifluoromethylcyclohexane-1,1-diacetic Acid (III, R = H).—Imide II (130 g, 0.5 mole) was dissolved in 360 ml of concentrated H_2SO_4 and allowed to stand overnight. H_2O (300 ml) was slowly added and the mixture was refluxed for 24 hr, diluted with 600 ml of H_2O, cooled, and filtered. The crude product was dissolved in a saturated $KHCO_3$ solution, treated with charcoal, and acidified with 10% HCl. Compound III, 90 g (67%), mp 161–164°, separated. Recrystallization of a small portion from H_2O or C_6H_6–petroleum ether (bp 37–54°) gave mp 163–164°. *Anal.* ($C_{11}H_{15}F_3O_4$) C, H, F.

3-Trifluoromethylcyclohexane-1,1-diacetic Acid Anhydride (IV).—The acid III (55 g, 0.2 mole) was refluxed with 300 ml of Ac_2O for 3 hr; the excess Ac_2O was vacuum distilled. Distillation of the residual oil (bp 140–145°, 0.2 mm) gave 43.5 g (87%) of product, mp 82–83° (ligroin). *Anal.* ($C_{11}H_{13}F_3O_3$) C, H, F.

Ethyl α-Cyano-α-(3-trifluoromethylcyclohexylidene)acetate (VII).—To 83 g (0.5 mole) of I in 50 ml of C_6H_6 was added 58 g (0.5 mole) of ethyl cyanoacetate and 1 ml of piperidine. The mixture was refluxed with a Dean–Stark water trap until no H_2O was collected. The reaction mixture was treated with 500 ml of H_2O containing 5 ml of concentrated HCl and extracted with three 200-ml portions of Et_2O, and the Et_2O extracts were washed (saturated $NaHCO_3$, saturated NaCl) and dried (Na_2SO_4). The Et_2O was removed *in vacuo*, and the product was distilled, 101–110° (0.07 mm), 113 g (87%). *Anal.* ($C_{12}H_{14}F_3NO_2$) C, H, N.

3-Trifluoromethylcyclohexane-1-carboxy-1-acetic Acid (VIII).—A solution of 113 g (0.43 mole) of VII in 1 l. of EtOH was mixed with 60 g (0.92 mole) of NaCN in 110 ml of H_2O. After standing for 3 days, all solvents were removed under reduced pressure. The dried powder was taken up in 750 ml of concentrated HCl and the mixture was refluxed for 24 hr, cooled, diluted with an equal volume of H_2O and allowed to stand overnight. The crude acid (63 g) was filtered, dissolved in 10% $KHCO_3$ solution, and treated with decolorizing carbon. After filtering, the solution was acidified with concentrated HCl and filtered (45 g, 41%), mp 151–152° (EtOAc–petroleum ether). *Anal.* ($C_{10}H_{13}F_3O_4$) C, H, F.

3-Trifluoromethylcyclohexane-1-carboxy-1-acetic Acid Anhydride (IX).—Compound VIII (20 g, 0.08 mole) was treated with Ac_2O as described under IV. Compound IX, 16.2 g (86%), was a colorless, viscous oil (bp 107–109°, 0.07 mm). *Anal.* ($C_{10}H_{11}F_3O_3$) C, H, F.

8-Trifluoromethyl-3-azaspiro[5.5]undecane-2,4-dione (V, R′ = H). Method A.—The anhydride IV (25 g) was mixed with excess concentrated aqueous NH_3 and slowly heated to 180°, driving off the excess NH_3 and H_2O. Cyclization occurred while heating at 180–200° for 15 min and gave a quantitative yield of product, mp 184–185° (acetone–H_2O). *Anal.* ($C_{11}H_{14}F_3NO_2$) C, H, N.

8-Trifluoromethyl-3-azaspiro[5.5]undecane (VI, R′ = H). Method B.—Finely powdered V (R′ = H) (21 g, 0.08 mole) was slowly added to a stirred solution of 12 g (0.27 mole) of $LiAlH_4$ in 1 l. of anhydrous Et_2O. When the initial reaction had subsided, the mixture was refluxed and stirred overnight. The mixture was decomposed by the slow dropwise addition of H_2O, filtered free of inorganic material, and dried (Na_2SO_4) overnight. The Et_2O was removed *in vacuo*, and the amine was distilled under reduced pressure to give 16.6 g (94%), bp 124–125° (23 mm). *Anal.* ($C_{11}H_{18}F_3N$) C, H, N.

The **hydrochloride** was prepared in the usual manner, mp 242–243°. *Anal.* ($C_{11}H_{19}ClF_3N$) Cl.

N-[3-(p-Fluorobenzoyl)propyl]-8-trifluoromethyl-3-azaspiro[5.5]undecane Hydrochloride (VI, R = $(CH_2)_3COC_6H_4F$).—Compound VI (R = H) (15.5 g, 0.07 mole) and 7.0 g (0.03 mole) of γ-chloro-*p*-fluorobutyrophenone was dissolved in 250 ml of toluene containing 0.5 g of KI and the mixture was refluxed for 24 hr. After cooling, the toluene solution was diluted with 1.5 l. of anhydrous Et_2O and refrigerated. The HCl of VI (R = H) was filtered (7.0 g). Alcoholic HCl (10 ml) was added to the filtrate and the mixture was refrigerated overnight. The product was filtered and dried, 12 g, mp 231–234°. Two recrystallizations from EtOH gave 7 g (55%) of product, mp 239–240°. *Anal.* ($C_{21}H_{28}ClF_4NO$) C, H, Cl, N.

N-(3-Dimethylaminopropyl)-8-trifluoromethyl-3-azaspiro[5.5]undecane-2,4-dione (V, R′ = $(CH_2)_3N(CH_3)_2$). Method C.—Dimethylaminopropylamine (40.8 g, 0.40 mole) was slowly added, with stirring, to 90 g (0.36 mole) of finely powdered anhydride IV. The mixture was heated on an oil bath at 180–200° for 1 hr. Cyclization of the amic acid intermediate was completed at the cessation of H_2O evolution. After cooling, the product was distilled, bp 140–145° (0.12 mm), 111.6 g (92%). *Anal.* ($C_{16}H_{25}F_3N_2O_2$) C, H, F, N.

N-(3-Dimethylaminopropyl)-8-trifluoromethyl-3-azaspiro[5.5]undecane (VI, R′ = $(CH_2)_3N(CH_3)_2$).—Compound V (R′ = $(CH_2)_3N(CH_3)_2$) (55 g, 0.16 mole), dissolved in 500 ml of anhydrous Et_2O, was slowly added with stirring to a solution of 20 g (0.42 mole) of $LiAlH_4$ dissolved in 1 l. of anhydrous Et_2O. The mixture was stirred overnight and decomposed, filtered, and dried (Na_2SO_4) as previously indicated under method B. The Et_2O was removed *in vacuo* and the product was distilled under reduced pressure to give 47.6 g (97%) of product, bp 92–100° (0.15 mm). *Anal.* ($C_{16}H_{29}F_3N_2$) C, H, F, N.

The **dihydrochloride** was prepared in the usual manner with alcoholic HCl, mp 308–309°. *Anal.* ($C_{16}H_{31}Cl_2F_3N_2$) Cl.

Diethyl 3-Trifluoromethylcyclohexane-1,1-diacetate (III, R = C_2H_5).—Compound III (R = H), (125 g, 0.47 mole) was refluxed in a mixture of 200 ml of absolute EtOH, 250 ml of C_6H_6, and 30 ml of concentrated H_2SO_4 for 8 hr. After working up in the usual manner, the product was distilled, bp 94–101° (0.15 mm), 119 g (79%). *Anal.* ($C_{15}H_{23}F_3O_4$) C, H.

1,1-Bis(β-hydroxyethyl)-3-trifluoromethylcyclohexane (XII).—A solution of 110 g (0.34 mole) of II (R = C_2H_5) in anhydrous Et_2O was slowly added with stirring to a solution of 30 g (0.63 mole) of $LiAlH_4$ in 1 l. of anhydrous Et_2O. After stirring and refluxing overnight, the mixture was decomposed with H_2O, stirred an additional 4 hr, and filtered. The filter cake was washed several times with 500-ml portions of Et_2O. The combined filtrates were dried (Na_2SO_4), and, after removal of the solvent *in vacuo*, a residue, 73.8 g (90%) of crude XII, was obtained. Recrystallization from EtAc and petroleum ether gave mp 51–52°. *Anal.* ($C_{11}H_{19}F_3O_2$) C, H.

8-Trifluoromethyl-3-oxaspiro[5.5]undecane (XIII).—The glycol XII (66 g, 0.27 mole) was treated with 300 ml of 48% HBr and the mixture was heated on a steam bath overnight. After cooling, it was poured into 300 ml of H_2O, neutralized with solid Na_2CO_3, and extracted three times with Et_2O. The ethereal extracts were combined and washed (dilute HCl, H_2O, saturated NaCl). After drying (Na_2SO_4), the Et_2O was removed *in vacuo*, and the residue was distilled, bp 87° (4 mm), 59.3 g (99%). *Anal.* ($C_{11}H_{17}F_3O$) C, H.

1,1-Bis(β-bromoethyl)-3-trifluoromethylcyclohexane (XIV).—Compound XIII (58 g, 0.26 mole) was dissolved in 300 ml of 48% HBr and 150 ml of concentrated H_2SO_4 was added in small portions with shaking and cooling. After heating at 100° for 24 hr, the mixture was cooled and poured into 1 l. of H_2O and extracted (three 200-ml portions of Et_2O). The Et_2O solution was washed (H_2O, saturated $NaHCO_3$, NaCl) then dried (Na_2SO_4). The Et_2O was removed *in vacuo*, and the residue was distilled, bp 118–120° (0.7 mm), 78.4 g (82%). *Anal.* ($C_{11}H_{17}Br_2F_3$) C, H, Br.

1,1-Bis(β-cyanoethyl)-3-trifluoromethylcyclohexane (XV).—A solution of 76 g (0.21 mole) of the dibromide XIV dissolved in 300 ml of EtOH was added rapidly with stirring to a solution of 35 g (0.54 mole) of KCN in 250 ml of 80% EtOH. The mixture was refluxed for 24 hr and poured into 2 l. of H_2O. The aqueous suspension was extracted with three 250-ml portions of Et_2O, and the extracts were combined, washed (H_2O), and dried (Na_2SO_4). After removal of the solvent *in vacuo*, the residue was distilled to yield 47 g (86%) of product, bp 154–157° (0.2 mm). *Anal.* ($C_{13}H_{17}F_3N_2$) C, H, N.

3-Trifluoromethylcyclohexane-1,1-dipropionic Acid (XVI, R = H).—Compound XV, 46.5 g (0.18 mole), was refluxed with 400 ml of concentrated HCl for 24 hr and then diluted with 400 ml of H_2O. The oil which separated could not be induced to crystallize and was extracted with Et_2O, treated with a saturated $KHCO_3$ solution, and reacidified. The acid was extracted with Et_2O and dried (Na_2SO_4), the solvent was removed *in vacuo* (50 mm), and on cooling the clear melt solidified into a glass (50 g, 95%) which could be induced to crystallize. *Anal.* ($C_{13}H_{19}F_3O_4$) C, H.

8-Trifluoromethylspiro[5.5]undecan-3-one (XVII).—Compound XVI (R = H) (49 g, 0.16 mole) was mixed with 5 g of

$Ba(OH)_2$ in a 300-ml flask equipped with a 20-cm column. On heating, some H_2O distilled above the melting point of the acid and active pyrolysis started at about 290°. The pressure was reduced to 250 mm and gradually to 2–3 mm as the reaction proceeded. A small amount of froth passed over into the receiving flask as the process continued. When no more distillate was obtained, the distillate was dissolved in 300 ml of Et_2O and washed (H_2O, $KHCO_3$, H_2O, NaCl). After drying (Na_2SO_4), the Et_2O was removed *in vacuo*, and the residue was distilled, bp 97–100° (0.6 mm), 17.3 g (50%). *Anal.* ($C_{12}H_{17}F_3O$) C, H.

8-Trifluoromethylspiro[5.5]undecane-3-ketoxime (XVIII).—A mixture of 10 g of $NH_2OH \cdot HCl$ and 12 g of NaAc was dissolved in the smallest volume of H_2O to give a clear solution. Compound XVII (9 g) was added with stirring and the mixture was shaken vigorously for 1 hr. After filtering, the crude product (9.5 g, mp 109–110°) was recrystallized from MeOH and then from EtAc, mp 115.5–116.5°. *Anal.* ($C_{12}H_{18}F_3NO$) C, H, N.

3-Amino-8-trifluoromethylspiro[5.5]undecane (XIX).—The oxime XVIII (8 g, 0.03 mole) was dissolved in anhydride Et_2O and was slowly added to a solution of 7 g (0.15 mole) of $LiAlH_4$ in 500 ml of anhydrous Et_2O. After stirring and refluxing for 6 hr the mixture was decomposed and filtered. The ethereal solution was dried (Na_2SO_4) and the Et_2O was removed *in vacuo*. Vacuum distillation of the residue gave the product (6 g, 86%), bp 77–79° (0.75 mm). Conversion in the usual manner gave the hydrochloride (alcoholic HCl), mp 293–296° (EtAc and EtOH). *Anal.* ($C_{12}H_{21}ClF_3N$) C, H, Cl, N.

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Studies on the Cholinergic Receptor. II.[1] Monosubstituted and Bicyclic Derivatives of *cis*-2-Methyl-4-dimethylaminomethyl-1,3-dioxolane Methiodide[2,3]

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In continuation of our studies on rigid analogs of acetylcholine, some 7-aza-2,4-dioxa-*cis*-bicyclo[3.3.0]octane methiodides (III) have been prepared. These are bicyclic analogs of the potent muscarinic agent *cis*-2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide (VI). For comparative purposes the *cis*- and *trans*-2-methyl-*cis*-4-dimethylaminomethyl-5-methyl-1,3-dioxolane methiodides (IV) have been prepared so that the effects of 5-methyl substitution could be determined. Muscarinic activities of these compounds were low but an inversion of geometric specificity, relative to *cis*- and *trans*-2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide, was noted with the 3,7-dimethyl-7-aza-2,4-dioxa-*cis*-bicyclo[3.3.0]octane methiodides, the *exo* isomer being more potent than the *endo* isomer by a factor of ten. This observation may be rationalized by assuming that the quaternary ammonium group constitutes the primary binding site in these compounds and thus determines the general mode of binding of the remaining molecular structure.

A fundamental problem in the analysis of structure–activity relationships is that of relating molecular structure to the relative geometry of the binding sites on the macromolecular receptive surface: this problem is particularly acute with small flexible molecules such as acetylcholine and some of its congeners where, despite the existence of preferred conformations in the crystalline and solution state, it is not possible to assume that these are also the conformations involved in binding at the receptor surface.[1,4] A partial solution to this problem may be obtained by the use of analogs of active molecules in which conformational rigidity predetermines the relative geometry of the proposed binding groups.

An important consideration in this general approach is that the molecular modification required to convert a flexible molecule into a rigid or semirigid analog should involve the minimum structural change in the active molecule. This point was discussed in part I of this series of papers and forms the basis for our choice of analogs of *cis*-2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide[5,6] (VI) in which reduced conformational flexibility may be achieved without the incorporation of additional potential binding groups.

In this paper we report the synthesis and muscarinic activities of 7-aza-2,4-dioxa-*cis*-bicyclo[3.3.0]octanes (III) which can duplicate one of the limiting conformations of the highly active agent VI. Since, in some ways, III is more analogous to a 2,4,5-trisubstituted 1,3-dioxolane, we have prepared for comparative purposes the 5-methyl derivative of VI, 2-methyl-*cis*-4-dimethylaminomethyl-5-methyl-1,3-dioxolane methiodide (IV), so that the effects of 5-methyl substitution on the activity of VI can be determined.

Chemistry.—The bicyclooctanes (III) were prepared by reaction between methylamine and the corresponding 4,5-*cis*-bischloromethyl-1,3-dioxolane (II) and subsequent quaternization of the formed tertiary amine with methyl iodide. The intermediate dioxolanes (II) were obtained[7] from *meso*-1,4-dichloro-2,3-dihydroxybutane[8] (I) and the appropriate aldehyde or ketone (Scheme I).

The chloromethyldioxolanes IIc and IId were obtained in admixture. Gas chromatography revealed two compounds in the ratio of 1:4 (peak areas) and this was confirmed by nmr spectroscopy. The nmr spec-

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