1-Trifluoromethyl-1,2,2-triphenylethylenes. Synthesis and Postcoital Antifertility Activity

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A number of 1-(trifluoromethyl)-1,2,2-triphenylethylenes have been synthesized by the reaction of fluoroolefins or arylfluoroolefins with arylorganometallic reagents, and the postcoital antifertility and uterotropic potencies have been determined. The most potent compound of this series is *trans*-*p*-methoxy-α-phenyl-α'-(trifluoromethyl)stilbene, which showed an ED_{50} of 0.013 mg/kg per day for both the antifertility and the uterotropic responses in female rats.

Many triphenylethylenes are known to possess estrogenic properties,[1] and several of them, including those that have an NO_2,[2] Cl,[3] or Et[4] group as a fourth substituent on the ethylene, have been investigated as antifertility agents. It was of interest to prepare triphenylethylene analogs containing F, since introduction of F into biologically active compounds can greatly alter activity.

Several triphenylethylenes bearing CF_3 substituents in various positions on the aromatic rings have already been prepared, but their estrogenicity was determined to be appreciably less than that of the corresponding unsubstituted compounds.[5]

We have synthesized a series of triphenylethylenes with CF_3 groups placed directly on the ethylene C. The postcoital and uterotropic activities of these 1-(trifluoromethyl)-1,2,2-triphenylethylenes have been determined.

Syntheses.—All the (trifluoromethyl)triphenylethylenes were prepared by the general reaction of fluoroolefins or arylfluoroolefins with PhLi or substituted phenyllithiums. A number of different fluoroolefins were used which were prepared by several different methods utilizing hexafluoropropene, chloropentafluoroacetone, or trifluorothioacetyl fluoride as the ultimate source of the CF_3 group.

The parent compound of this series, 1-(trifluoromethyl)-1,2,2-triphenylethylene (**1**), and 3 substituted analogs (**2**, **3**, and **6** of Table I) were prepared by the stepwise replacement of the vinylic F atoms of hexafluoropropene with aryl groups from ArLi reagents (Scheme I).

The first step of this series of reactions yields two isomeric forms (cis and trans) of a 1-arylperfluoropropene. The preparation of 1-phenylperfluoropropene by this method was reported previously, but only one isomer was isolated and its stereochemical structure was not determined.[6] We have found that both isomers are formed, with the trans isomer predominating.

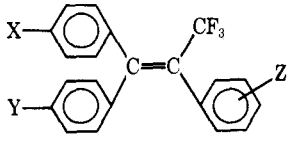
To prepare the unsubstituted parent compd **1**, it was not necessary to separate the isomers since they both lead to **1** after reaction with PhLi. By using only the pure trans isomer, however, it was possible to prepare isomerically pure triphenylethylenes with different aryl substituents on the 2-C atom of the ethylene because the replacement of the vinylic F atoms is stereospecific without inversion. The stereospecificity of these reactions was shown by the fact that only the *cis*-stilbene **49** is formed when **53** is treated with PhLi, and that 2 different isomeric triphenylethylenes (**2** and **3**) are formed by adding PhLi and p-$CH_3OC_6H_4Li$ in a different order to hexafluoropropene.

1-(Trifluoromethyl)-1,2,2-triphenylethylene (**1**) was also prepared as shown in Scheme II by treating PhLi with 1,1-diphenylperfluoropropene (**51**). This diphenylethylene (**51**) was formed by the reaction of trifluorothioacetyl fluoride[7] with diphenyldiazomethane.

By substituting p-(perfluoroisopropyl)phenyllithium for PhLi in this reaction scheme, the triphenylethylene **13** (Table I) was prepared, and by substituting penta-

TABLE I

TRIPHENYLETHYLENES. POSTCOITAL ANTIFERTILITY AND UTEROTROPIC POTENCIES IN FEMALE RATS



No.	X	Y	Z	Antifertility oral ED_{50} ± SE, mg/kg per day	Uterotropic oral ED_{50} ± SE, mg/kg per day
1	H	H	H	0.12 ± 0.04	0.12 ± 0.04
2	CH_3O	H	H	0.013 ± 0.004	0.013 ± 0.004
3	H	CH_3O	H	0.040 ± 0.009	0.040 ± 0.009
4	H	H	p-CH_3O	0.12 ± 0.04	0.12 ± 0.04
5	CH_3O	CH_3O	H	0.12 ± 0.04	0.12 ± 0.04
6	F	H	H	0.31 ± 0.54	0.31 ± 0.54
7	H	H	p-F	0.040 ± 0.009	0.040 ± 0.009
8	CH_3O	H	p-F	0.020 ± 0.010	0.020 ± 0.010
9	H	H	m-F	0.16 ± 0.04	0.16 ± 0.04
10	H	H	o-F	0.16 ± 0.04	0.16 ± 0.04
11	H	H	p-CF_3	0.030 ± 0.010	0.030 ± 0.010
12	H	H	m-CF_3	0.030 ± 0.010	0.030 ± 0.010
13	H	H	p-$CF(CF_3)_2$	0.16 ± 0.04	0.16 ± 0.04
14	H	H	p-Cl	0.030 ± 0.010	0.030 ± 0.010
15	H	H	p-CH_3	0.48 ± 0.16	0.62 ± 0.14
16	H	H	a	0.82 ± 0.26	0.82 ± 0.26
17[b]	H	H	H	0.20 ± 0.07	0.20 ± 0.07
52	1,1,2-Triphenyl-2-trifluoroethane			0.98 ± 0.66	1.6 ± 1.0
	Diethylstilbestrol			0.012 ± 0.002	0.015 ± 0.002

[a] C_6H_4Z = 2-thienyl. [b] CF_3 on ethylene replaced by C_2F_5.

(1) J. Grundy, *Chem. Rev.*, **57**, 281 (1957).

(2) M. R. Callantine, R. R. Humphrey, S. L. Lee, B. L. Windsor, N. H. Scholtin, and O. P. O'Brien, *Endocrinology*, **79**, 153 (1966).

(3) D. E. Holtkamp, J. G. Greslin, G. A. Root, and L. J. Lerner, *Proc. Soc. Exp. Biol. Med.*, **105**, 197 (1960).

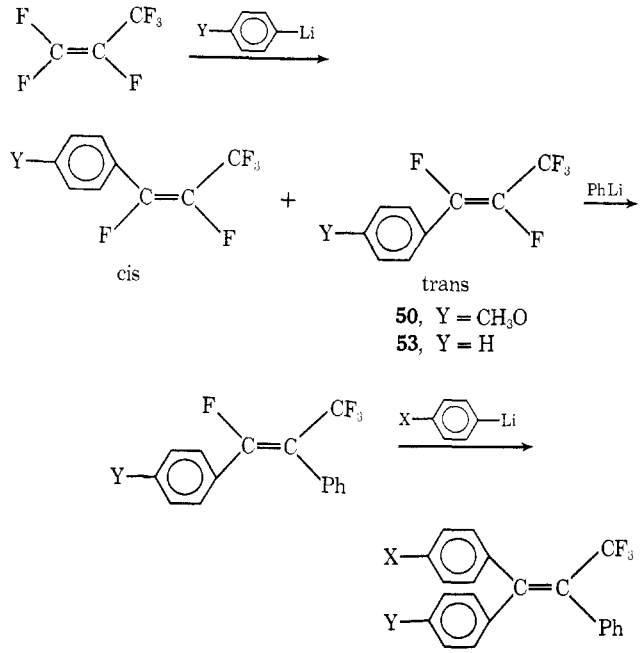
(4) M. J. K. Harper and A. L. Walpole, *Nature (London)*, **212**, 87 (1966).

(5) N. P. Buu-Hoï, N. H. Nam, and N. D. Xuong, *Recl. Trav. Chim. Pays-Bas*, **85**, 367 (1966).

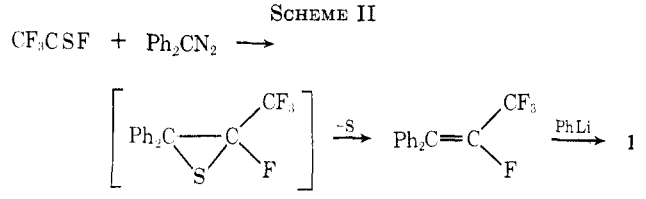
(6) S. Dixon, *J. Org. Chem.*, **21**, 400 (1956).

(7) W. J. Middleton, E. G. Howard, and W. H. Sharkey, *ibid.*, **30**, 1375 (1965).

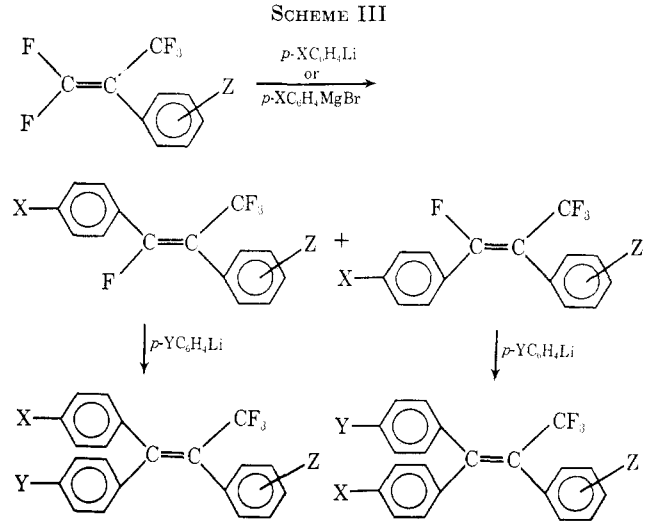
SCHEME I



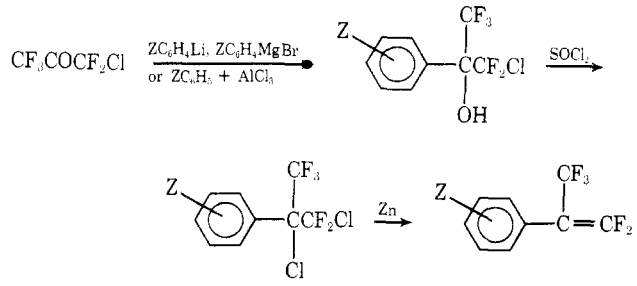
SCHEME II



SCHEME III



SCHEME IV



fluorothiopropionyl fluoride[7] for CF_3CSF, (pentafluoroethyl)triphenylethylene (**17**) was obtained.

The majority of the (trifluoromethyl)triphenylethylenes were prepared by reaction of arylorganometallic reagents with 2-arylperfluoropropenes, as illustrated in Scheme III.

The 2-arylperfluoropropenes were prepared from chloropentafluoroacetone in 3 steps, as illustrated in Scheme IV. The ketone was first converted to the benzyl alcohol, either by addition of an ArLi or Grignard reagent, or by a Friedel–Crafts reaction with substituted benzene. The OH was then replaced with Cl by treatment with $SOCl_2$, and then dechlorination with Zn gave the olefin.

By using this method (Schemes IV and III), ten triphenylethylenes containing a variety of substituents on the Ph rings were prepared (Table V). 1-(Trifluoromethyl)-1-thienyl-2,2-diphenylethylene (**16**) was also obtained similarly.

The (trifluoromethyl)triphenylethylenes show a surprising chemical stability, with no isomerization occurring when they are treated with aq acids or bases. However, they are easily reduced to the ethane, even by mild reducing agents such as aq HI.

Pharmacology.—Postcoital antifertility and uterotrophic activities in the rat were determined using a method developed by Strauss.[8] Immature female Holtzman rats (28 days old) were induced into precocious puberty with a single dose of pregnant mare's serum gonadotropin and were mated with normal males during the night of day 30–31. Compds were given orally after mating once each day for 6 days by intubation of 0.2 ml of a suspension in sesame oil to groups of 4 rats starting on the day of finding sperm or a vaginal plug (day 31) and ending 5 days later (day 36). The dose increment was 4X. The rats were killed by CO_2 asphyxiation on day 38 and their uteri were examined for implantation sites. If any sites were found they were considered pregnant. (Control pregnant rats had a mean of 8 implantation sites). The number of rats having visibly thickened uteri was noted. With 2 exceptions in 80 instances, rats protected from pregnancy by these compds also had thickened uteri. ED_{50} values and their standard errors[9] were estimated from log–probit plots of daily oral dose *vs.* per cent of rats protected from pregnancy or per cent of rats having thickened uteri.

As can be seen from the data in Table I, many of the (trifluoromethyl)triphenylethylenes are quite potent, both as postcoital antifertility agents and as estrogens (uterotropic agents) though none was more potent than diethylstilbestrol. The ED_{50}'s for both effects in all the compounds tested were either identical or very close together; the observed correlation is most probably a reflection of relative estrogenic potency.

Some interesting structure–activity relationships were noted. The introduction of a *p*-CH_3O group in the Ph ring cis to the CF_3 group (**2**) greatly increased potency over the unsubstituted parent compd (**1**). The introduction of *p*-CH_3O in the trans ring (**3**) also increased potency by a less marked degree, resulting

(8) W. F. Strauss, Ph.D. Thesis, University of Wisconsin, "Neural Timing of Ovulation in Immature Rats Treated with Gonadotropin," University Microfilms, Ann Arbor, Mich., Order No. 64-7104; *Diss. Abstr. B*, **24**, 4764 (1964).

(9) L. C. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.*, **57**, 261 (1944).

in a different degree of activity for the two isomers (**2** and **3**). The substitution of a *p*-CH_3O group into the 1-Ph ring had no effect on potency. Other groups in the 1-Ph ring, including *p*-F, *p*- and *m*-CF_3, and *p*-Cl increased potency whereas *o*- and *m*-F, *p*-$CF(CF_3)_2$, and *p*-CH_3 decreased potency. Replacement of the 1-CF_3 group with C_2F_5 slightly decreased potency, but replacement of the 1-Ph ring with a thienyl group greatly decreased potency. Reduction of the double bond also greatly decreased potency.

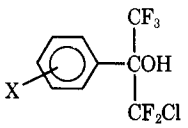
The most potent compd of this series is *trans*-*p*-methoxy-α-phenyl-α'-(trifluoromethyl)stilbene (**2**).

Experimental Section

Chemical Procedures.—The following synthetic procedures are representative for preparation of compds in Tables II–V.

TABLE II

BENZYL ALCOHOLS DERIVED FROM CF_3COCF_2Cl

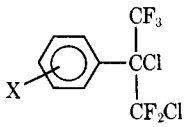


No.	X	Procedure	Bp (mm), °C	Yield, %	Formula	Anal.
18	H	A	76–77 (11.2)	77	$C_9H_6ClF_5O$	C, H, Cl, F
19	*p*-OCH_3	A	120–35 (8.0)[a]	65	$C_{10}H_8ClF_5O_2$	Cl, F
20	*p*-F	A	75–76 (9.0)	56	$C_9H_5ClF_6O$	C, H, F
21	*m*-F	A	72 (8.8)	36	$C_9H_5ClF_6O$	C, H, Cl, F
22	*o*-F	B[b]	80–82 (8.9)	14	$C_9H_5ClF_6O$	C, H, Cl, F[c]
23	*p*-CF_3	B	79–80 (10.6)	64	$C_{10}H_5ClF_8O$	C, H, Cl, F
24	*m*-CF_3	A	75–76 (9)	30	$C_{10}H_5ClF_8O$	C, H, Cl, F
25	*p*-Cl	C	84 (6.2)	39	$C_9H_5Cl_2F_5O$	C, H, Cl
26	*p*-CH_3	C	60–61 (2.1)	83	$C_{10}H_8ClF_5O$	C, H, Cl, F
27	*d*	B	71–72 (10.2)	73	$C_{10}H_4Cl_2F_{10}O_2S$	C, H, Cl, F

[a] Mp 80–81°, recrystd from hexane. [b] Reaction run at −78° in THF. [c] Calcd: C, 38.80; F, 40.92. Found: C, 39.35; F, 39.39. [d] C_4H_6X = 2-thienyl.

TABLE III

BENZYL CHLORIDES. PREPARED BY PROCEDURE D



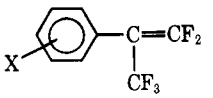
No.	X	Run time, days	Bp (mm), °C	Yield, %	Formula	Anal.
28	H	3	69–70 (7.8)	79	$C_9H_5Cl_2F_5$	C, H, Cl, F
29	*p*-OCH_3	2.3	101–102 (4.0)	69	$C_{10}H_7Cl_2F_5O$	C, H, Cl
30	*p*-F	3	73–74 (8.0)	77	$C_9H_4Cl_2F_6$	C, H, Cl, F
31	*m*-F	21[a]	89–90 (33)	66	$C_9H_4Cl_2F_6$	
32	*o*-F	2.8	73–75 (7.4)	80	$C_9H_4Cl_2F_6$	C, H, F[b]
33	*p*-CF_3	4	81–82 (12.8)	29	$C_{10}H_4Cl_2F_8$	C, H, Cl
34	*m*-CF_3	7	67–68 (8.3)	81	$C_{10}H_4Cl_2F_8$	C, H, F[c]
35	*p*-Cl	4	91 (7.8)	50	$C_9H_4Cl_3F_5$	C, H, Cl, F
36	*p*-CH_3	2.7	57 (1.4)	40[d]	$C_{10}H_7Cl_2F_5$	
37	*e*	1.1	73–75 (14)	37	$C_7H_3Cl_2F_5S$	C, H, F, S

[a] Addl $SOCl_2$ and pyridine added on 14th day. [b] Calcd: C, 36.39; Found: 36.91. [c] Calcd: F, 43.80. Found: F, 44.32. [d] 95% pure, as detd by nmr and glc; other product was *p*-(chloromethyl)-α-(chlorodifluoromethyl)-α-(trifluoromethyl)benzyl chloride. [e] C_6H_4X = 2-thienyl.

Melting points are uncorrected and were determined with a Mel-Temp capillary melting point apparatus. PhLi used was a 2 *M* commercial soln in Et_2O–PhH (30:70); BuLi was a commercial soln (1.65 *M*) in hexane; PhMgBr was a commercial soln in Et_2O. Where analyses are indicated only by symbols of the elements, results do not deviate more than ± 0.4% from calculated. Products were identified by ^{19}F and ^1H nmr, ir, and uv spectra. Representative data are given for each class of compd. All ^{19}F nmr spectra were run with CCl_3F internal std.

TABLE IV

STYRENES. PREPARED BY PROCEDURE E



No.	X	Solvent	Bp (mm), °C[a]	Yield, %	Formula	Anal.
38	H	MeOH	130–131	71	$C_9H_5F_5$	
39	*p*-OCH_3	MeOH	75–76 (9)	82	$C_{10}H_7F_5O$	C, H, F
40	*p*-F	MeOH	134.5–135	77	$C_9H_4F_6$	C, H
41	*m*-F	THF	130–133	47	$C_9H_4F_6$	F
42	*o*-F	THF	130–132	71	$C_9H_4F_6$	C, H
43	*p*-CF_3	MeOH	146–147	36	$C_{10}H_4F_8$	C, H, F
44	*m*-CF_3	THF	141–142	64	$C_{10}H_4F_8$	C, H, F[c]
45	*p*-Cl	MeOH	63–66 (20)	73	$C_9H_4ClF_5$	
46	*p*-CH_3	MeOH	54–55 (20)	79	$C_{10}H_7F_5$	C, H, F
47	*b*	MeOH	128–130	44	$C_7H_3F_5S$	C, H, F, S

[a] Unless otherwise noted, distn was carried out at ambient pressures. [b] C_6H_4X = 2-thienyl. [c] Calcd: C, 43.50. Found: 43.96.

TABLE V

TRIARYLETHYLENES

No.	Formula	Anal.	Procedure	Bp (mm), °C	Mp, °C	Yield, %[a]
1	$C_{21}H_{15}F_3$	C, H, F	H	*b*	83–85	56
	$C_{21}H_{15}F_3$		G	150–155 (2)	80–84	7.0
2	$C_{22}H_{17}F_3O$	C, H, F	G	130–160 (0.1–0.25)	73–74.5	27[c]
3	$C_{22}H_{17}F_3O$	C, H, F	G	140–145 (0.25)	60–65	4.4
4	$C_{22}H_{17}F_3O$	C, H, F	F	160 (0.25)	100–101	28
5	$C_{23}H_{19}F_3O_2$	C, H, F[d]	F	147–166 (0.25)		14
6	$C_{21}H_{14}F_4$	C, H, F	G	118–120 (0.15)	83–84	27
7	$C_{21}H_{14}F_4$	C, H, F	F	127–131 (0.3)	77–79	25
8	$C_{22}H_{16}F_4O$	C, H, F	F	140–155 (0.3)	125–127	16
9	$C_{21}H_{14}F_4$	C, H, F	F	140 (0.5)	110–111	25
10	$C_{21}H_{14}F_4$	C, H, F	F	130–137 (0.55)	84.5–86	51
11	$C_{22}H_{14}F_6$	C, H, F	F	*b*	111–113	31
12	$C_{22}H_{14}F_6$	C, H, F	F	128–130 (0.8)	83–85	32
13	$C_{24}H_{14}F_{10}$	C, H, F	H	128–129 (0.4)	60–62	67
14	$C_{21}H_{14}ClF_3$	C, H, F, Cl	F	140–170 (0.6)	101–102	31
15	$C_{22}H_{17}F_3$	C, H, F, Cl	F	140–145 (0.6)	92–93	31
16	$C_{19}H_{13}F_3S$	C, H, F, S	F	140–142 (0.8)	77–80	15
17	$C_{22}H_{15}F_5$	C, H, F	H	*b*	89–90	15[e]

[a] Unless otherwise noted yield given refers to final synthesis step in each case, after recrystn. [b] Not distd. [c] Not recrystd. [d] See text. [e] Overall yield.

Procedure A. α-(Chlorodifluoromethyl)-*p*-fluoro-α-(trifluoromethyl)benzyl Alcohol (20).—A 70-ml sample (meas at −78°, *ca.* 0.65 mole) of chloropentafluoroacetone was distd into a stirred soln of *p*-(fluorophenyl)magnesium bromide (prepd from 0.5 g-atom of Mg turnings and 0.5 mole of *p*-bromofluorobenzene in 400 ml of Et_2O) at 25°. The mixt was stirred at 25° for 1 hr and poured into 300 ml of 10% HCl. The Et_2O layer was sepd, washed (H_2O), dried ($MgSO_4$), and distd to give 78.0 g of **20** as a colorless liquid: bp 75–76° (9 mm); $n^{25}D$ 1.4305; ^{19}F nmr (CCl_3F) δ 62.2 (m, 2 F), 73.8 (t, J = 11 Hz, 3 F), 111.6 ppm (m, 1 F).

Procedure B. α-(Chlorodifluoromethyl)-α,*p*-bis(trifluoromethyl)benzyl Alcohol (23).—A 100-g sample (0.445 mole) of *p*-bromobenzotrifluoride was added dropwise to a soln of 0.4 mole of BuLi in 250 ml of hexane and 400 ml of Et_2O at 10°. A 50-ml sample (meas at −78°) of chloropentafluoroacetone was distd into the mixt at 5–10°. The reaction mixt was worked up as for **20** and distd to give 84.8 g of **23** as a colorless liquid: bp 79–80° (10.6 mm); $n^{25}D$ 1.4104.

Procedure C. *p*-Chloro-α-(chlorodifluoromethyl)-α-(trifluoromethyl)benzyl Alcohol (39).—A 1400-ml Hastelloy-lined bomb, charged with 392 g (3.5 mole) of PhCl, 7.0 g of anhyd $AlCl_3$, and 160 g (0.88 mole) of chloropentafluoroacetone was heated for 8 hr at 200°. The mixt was cooled, filtered, and distd twice to give 100.6 g of **39** as a pale yellow liquid.

***p*-Methyl-α-(chlorodifluoromethyl)-α-(trifluoromethyl)benzyl alcohol (26)** was prepd as for **39** except that the bomb was heated 8 hr at 120°.

Procedure D. *p*-Chloro-α-(chlorodifluoromethyl)-α-(tri-

fluoromethyl)benzyl Chloride (14).—A mixt of 78.6 g (0.266 mole) of the benzyl alcohol **25**, 100 ml of $SOCl_2$, and 3 ml of pyridine was refluxed 96 hr. H_2O was added dropwise to the cooled mixt and the product was extd with CCl_3F. The org layer was washed with 5% NaOH and H_2O to remove unreacted alcohol, dried ($MgSO_4$), and distd to give 42.9 g of **14** as a colorless liquid: bp 91° (7.8 mm); ^{19}F nmr (CCl_3F) δ 55.1 (m, 2 F), and 68.3 ppm (t, J = 12 Hz, 3 F).

Reaction times necessary for complete conversion varied and reactions were usually followed by glc.

Procedure E. β,β-Difluoro-*p*-methoxy-α-(trifluoromethyl)styrene (39).—A soln of 51.0 g (0.165 mole) of α-(chlorodifluoromethyl) *p*-methoxy-α-(trifluoromethyl)benzyl alcohol in 50 ml of MeOH was added dropwise to a stirred suspension of 20 g of Zn dust and 1 g of anhyd $ZnCl_2$ in 200 ml of MeOH. The reaction mixt was filtered and the filtrate was mixed with H_2O and extd with CCl_3F. The exts were washed (H_2O), dried ($MgSO_4$), and distd to give 32.3 g of **39** as a colorless liquid: bp 75–76 (9 mm); $n^{25}D$ 1.4438; ir (liq) 5.76 μ (C=CF_2); ^{19}F nmr (CCl_3F) δ 60.2 (d, J = 24 Hz, to d, J = 11 Hz, 3 F), 77.4 (quartet, J = 24 Hz, to d, J = 15 Hz, 1 F), and 79.2 ppm (d, J = 15 Hz, to quartets, J = 11 Hz, 1 F).

When THF was the solvent, the reaction mixt was refluxed for 1 hr.

Procedure F. 1-(Trifluoromethyl)-1-*m*-(trifluoromethyl)-phenyl-2,2-diphenylethylene (12).—A soln of 0.092 mole of PhLi was added dropwise to a soln of 12.8 g (0.046 mole) of 2-(*m*-(trifluoromethyl)phenyl)pentafluoro-1-propene in 75 ml of Et_2O cooled to 5–10°. The reaction mixt was mixed with 100 ml of 5% HCl; the org layer was sepd, washed (H_2O), dried ($MgSO_4$), and distd to give 8.2 g of a dark-red oil, bp 128–130° (0.8 mm). Chromatog over Al_2O_3 with pentane and recryst from pentane gave **12** as colorless crystals: mp 83–85°; uv (EtOH) λ_{max} 263 (ϵ 8600) and 223 mμ (19,600); ^{19}F nmr (CCl_3F) δ 56.3 (s, 3 F) and 63.7 ppm (s, 3 F).

Syntheses of **4**, **9**, **10**, **11**, **14**, **15**, and **16** were carried out as for **12**.

1-(Trifluoromethyl)-2,2-bis(*p*-methoxyphenyl)-1-phenylethylene (5).—To a soln of *p*-methoxyphenyllithium in Et_2O–hexane (prepd from 0.25 mole of *p*-bromoanisole and 0.225 mole of BuLi) was added 15.6 g (0.075 mole) of 2-phenylpentafluoro-1-propene dropwise at 0°. The reaction mixt was worked up as for **12** and distd to give 10.1 g of semisolid, mp 115–120° (0.1 mm). The product was filtered; the ppt was nearly pure *trans*-*p*-methoxy-α'-fluoro-α-(trifluoromethyl)stilbene (**54**), and the filtrate has a 62:38 cis:trans isomer mixt.

A soln of 5.93 g (0.02 mole) of the isomer mixt in 15 ml of Et_2O was added dropwise to a soln of *p*-methoxyphenyllithium (from 0.02 mole of BuLi and 5.61 g of *p*-bromoanisole in ether–hexane) at 25°. The mixt was worked up as for **12** and distd to give 1.1 g (14%) of **5** as a viscous orange syrup. Minor impurities appeared in the ^{19}F nmr spectrum. *Anal.* Calcd ($C_{23}H_{19}F_3O_2$): H, F; C, calcd 71.86; found, 70.84.

4,α'-Difluoro-α-(trifluoromethyl)stilbene (48 and 55).—A mixt of 22.6 g (0.1 mole) of p,β,β-trifluoro-α-(trifluoromethyl)-styrene and 0.15 mole of PhMgBr in 50 ml of Et_2O was stirred 20 hr at 25°. It was worked up as for **12** and distd to give 14.0 g (50%) of a mixt of cis and trans isomers of 4,α'-difluoro-α-(trifluoromethyl)stilbene as a semisolid mass, bp 80–89° (0.25 mm). The solid was filtered off and recryst twice from pentane to give 5.3 g (19%) of the cis isomer (**55**) as colorless needles: mp 67–69°; ^{19}F nmr δ 59.2 (d, J = 24 Hz, 3 F) 91.7 ppm (quartet, J = 24 Hz, 1 F) and 112.1 ppm (m, 1 F). *Anal.* ($C_{15}H_9F_5$) C, H, F.

The liquid portion was redistd to give 6.50 g (23%) of the trans isomer (**48**) as a colorless liquid: bp 87–89° (0.25 mm); ^{19}F nmr δ 56.6 (d, J = 11 Hz, 3 F) 76.2 (quartet, J = 11 Hz, 1 F), and 112.7 ppm (m, 1 F). *Anal.* ($C_{15}H_9F_5$) C, H, F.

1-(Trifluoromethyl)-1-(*p*-fluorophenyl)-2,2-diphenylethylene (7).—A soln of 0.02 mole of PhLi was added dropwise to a stirred soln of 5.7 g (0.02 mole) of 4,α'-difluoro-α-(trifluoromethyl)-stilbene (mixt of isomers **48** and **55**) in 25 ml of Et_2O at 25°. The mixt was worked up as for **12** and distd to give 2.1 g of **7** as a colorless liquid which solidified on cooling.

***trans*-4-Fluoro-4'-methoxy-α'-phenyl-α-(trifluoromethyl)-stilbene (8).**—A soln of 4.3 g (0.015 mole) of *cis*-4,α'-difluoro-α-(trifluoromethyl)stilbene (**55**) was added dropwise to a soln of *p*-methoxyphenyllithium (prepd from 0.2 mole of *p*-bromoanisole and 0.016 mole of BuLi in Et_2O–hexane) at 25°. The mixt was worked up as for **12** and distd to give 1.2 g of colorless liquid that solidified on cooling. Recrystn from pentane gave 0.90 g of **8** as colorless prisms.

Procedure G. 1-Phenylpentafluoropropene prepared according to Dixon,[6] bp 140–151°, was found to be 17:83 mixt of cis and trans isomers. The pure trans form **53** was isolated by distn as the higher boiling fraction: bp 150–151°; $n^{25}D$ 1.4433; uv (EtOH) λ_{max} 245 mμ (ϵ 18,000); ^{19}F nmr (CCl_3F) δ 68.7 (d, J = 22.3 Hz to d, J = 10 Hz, CF_3), 146.9 (d, J = 133 Hz to quartet J = 22.3 Hz αF), 170.1 ppm (d, J = 133 Hz to quartet, J = 10 Hz, βF).

The pure cis form **57** was isolated after distn by prep glc on a fluorosilicone column and was obtd as a colorless liquid: bp 141°; $n^{25}D$ 1.4311; uv (EtOH) λ_{max} 233 mμ (ϵ 8940); ^{19}F nmr (CCl_3F) δ 66.3 (d, J = 8 Hz, to d, J = 13 Hz 3 F), 109.7 (d, J = 8 Hz to quartet, J = 8 Hz, 1 F), 155.1 ppm (d, J = 8 Hz to quartet, J = 13 Hz, 1 F).

***cis*-1,2-Diphenyltetrafluoropropene (49).**—A soln of 0.16 mole of PhLi was added dropwise to a stirred soln of 31.2 g (0.15 mole) of *trans*-1-phenylpentafluoropropene (**53**) in 200 ml of Et_2O cooled in a Dry Ice–Me_2CO bath. The reaction mixt was warmed to 25°, worked up as for **12** above, and distd to give two main fractions.

The lower boiling fraction, bp 117–119° (5 mm), 12 g, partially solidified on cooling. Recryst from pentane gave 8.1 g (20%) of **49** as colorless crystals (rods): mp 43–44°, uv (EtOH) λ_{max} 254 mμ (ϵ 11,300); ^{19}F nmr (CCl_3F) δ 58.8 (d J = 24 Hz, 3 F), 93.1 ppm (quartet, J = 24 Hz, 1 F).

(**1**) The higher boiling fraction, bp 150–155° (2 mm), also solidified on cooling. Recryst from pentane gave 1.8 g of **1** as colorless crystals, mp 80–84°.

***trans*-*p*-Methoxy-α-phenyl-α'-(trifluoromethyl)stilbene (2).**—A soln of 5.32 g (0.02 mole) of *cis*-1,2-diphenyltetrafluoropropene in 5 ml of Et_2O was added dropwise to a soln of *p*-methoxyphenyllithium (prepd from 0.35 g of Li and 5.61 g of *p*-bromoanisole) in 30 ml of ether at 25°. The reaction mixt was worked up as for **12**, and distd to give 1.9 g of liq that solidified on cooling. Recrystn from pentane gave **2** as a colorless solid.

1-(Trifluoromethyl)-2-(*p*-fluorophenyl)-1,2-diphenylethylene (6).—To a soln of 4-fluorophenyllithium (prepd from 0.06 mole of BuLi and 12.3 g (0.07 mole) of 1-bromo-4-fluorobenzene in 100 ml of Et_2O) was added a soln of 13.3 g (0.05 mole) of **49** in Et_2O. The mixt was worked up as for **12** and distd.

***cis*-*p*-Methoxy-α-phenyl-α'-(trifluoromethyl)stilbene (3).**—Hexafluoropropene (*ca.* 0.2 mole) was distd slowly into a soln of *p*-methoxyphenyllithium (prepd from 0.33 mole of *p*-bromoanisole and 0.32 mole of BuLi in 50 ml of Et_2O) at −78°. The reaction mixt was warmed to 0°, worked up as for **12**, and distd to give 3 main fractions.

Fraction A, 17.3 g, was shown to be a mixt of 21% *cis*- and 79% *trans*-1-*p*-(methoxyphenyl)pentafluoropropene by its ^{19}F nmr spectrum: bp 62–68° (1.0 mm); ^{19}F nmr (CCl_3F) for cis isomer only δ 66.1 (d, J = 13 Hz, to d, J = 9 Hz, 3 F), 108.1 (m, αF), 175.7 ppm (quartet, J = 13 Hz, to d, J = 10 Hz, βF).

Fraction B, 20.2 g (42%), was pure *trans*-1-(*p*-methoxyphenyl)-pentafluoropropene (**50**): bp 68–69° (1.0 mm); ^{19}F nmr (CCl_3F) δ 67.3 (d, J = 22 Hz, to d, 11 Hz, 3 F) 140.2 (d, J = 130 Hz, to quartet, J = 22 Hz, αF), 173.0 ppm (d, J = 130 Hz, to quartet J = 11 Hz, βF). *Anal.* ($C_{10}H_7F_5O$) C, H, F.

Fraction C, 3.3 g, was a by-product, *trans*-1-(5-bromo-2-methoxyphenyl)pentafluoropropene (**56**): bp 94–95° (1.0 mm); ^{19}F nmr (CCl_3F) δ 68.1 (d, J = 21 Hz to d, J = 11 Hz, 3 F), 133.2 (d, J = 139 Hz to q, J = 11 Hz, 1 F), and 165.7 ppm (d, J = 139 Hz to q, J = 11 Hz, 1 F). *Anal.* ($C_{10}H_6BrF_5O$) C, H, Br, F.

A 16.0-g sample (0.0645 mole) of **50** was added dropwise to a soln of 0.16 mole of PhLi at 25°. The mixt was worked up as for **12** and distd to give 9.0 g of dark, viscous syrup, bp 140–155° (0.25 mm). Chromatog on neutral Al_2O_3 with pentane and Et_2O–pentane gave 1.0 g of **3** as colorless crystals.

Procedure H. 1,1-Diphenyltetrafluoropropene (51).—Perfluorothioacetyl fluoride[7] was bubbled into a rapidly stirred soln of diphenyldiazomethane[10] (prep from 0.1 mole of benzophenone hydrazone and 0.1 mole of yellow HgO) in pentane at 0° until the purple color was discharged. The soln was distd to give 15 g (56%) of **51** as a colorless liquid: bp 80° (1.7 mm). *Anal.* ($C_{15}H_{10}F_4$) C, H, F.

1-(Trifluoromethyl)-1,2,2-triphenylethylene (1).—A soln of

(10) W. J. Middleton and W. H. Sharkey, *J. Org. Chem.*, **30**, 1384 (1965).

0.29 mole of PhLi was added dropwise to a stirred soln of 6.66 g (0.25 mole) of 1-fluoro-1-trifluoromethyl-2,2-diphenylethylene in 20 ml of Et_2O cooled in ice. The reaction mixt was worked up as for **12** and the solvent was evaporated. The product was recrystd from pentane to give 4.5 g as colorless crystals.

1-Trifluoro-1-(*p*-perfluoroisopropylphenyl)-2,2-diphenylethylene (13).—To a soln of 0.04 mole of BuLi in 25 ml of hexane and 25 ml of Et_2O at 0° was added 14.3 g (0.044 mole) of *p*-bromo(perfluoroisopropyl)benzene[11] in 25 ml of Et_2O. After 30 min, 9.0 g of **51** was added dropwise at 0–10°. The reaction mixt was stirred overnight and filtered and the filtrate was distd to give 11.1 g of **13** as a colorless, viscous liquid, bp 128–129° (0.4 mm), that solidified on cooling.

1,1,2-Triphenylperfluoro-1-butene (17).—A sample of 6.1 g (0.34 mole) of perfluorothiopropionyl fluoride[7] was slowly distd into a dry, stirred soln of diphenyldiazomethane[10] (from 0.34 mole of benzophenone hydrazone) in pentane at 5°. The reaction mixt was distd, bp 98° (0.55 mm), to give a mixt of 1 part of 1,1-diphenylperfluoro-1-butene to 4 parts of 2-fluoro-2-perfluoroethyl-3,3-diphenylthiirane (identified by ^{19}F nmr spectrum). To a soln of this mixt in Et_2O at 0° was added 0.045 mole of PhLi in 21 ml of Et_2O–PhH. The mixt was worked up in the usual manner, the solvent was evapd, and the residue was recrystd from pentane to give 2.0 g of **17** as colorless crystals.

Procedure I. 1-(Trifluoromethyl)-1,2,2-triphenylethane (52).—A mixt of 2.88 g (8.8 mmole) of 1-(trifluoromethyl)-1,2,2-triphenylethylene (**1**) and 30 ml of 57% HI was heated at reflux 18 hr and cooled. The solid that formed was filtered off, washed (H_2O), and recrystd from heptane (a little solid $NaHSO_3$ was used to remove the I_2 color) to give 2.21 g (77%) of **52** as colorless crystals: mp 102–103°; ^{19}F nmr (CCl_3F) δ 64.5 ppm (d, J = 8 Hz, 3F); ^1H nmr (CCl_3F) τ 2.5–3.2 (m, 15 H) 5.38 (d, J = 12 Hz, 1 H) 5.80 (d, J = 12 Hz to quartets, J = 8 Hz, 1 H). *Anal.* ($C_{21}H_{17}F_3$) C, H, F.

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Synthesis and Hormonal Activities of 8-L-Homolysine-vasopressin[1]

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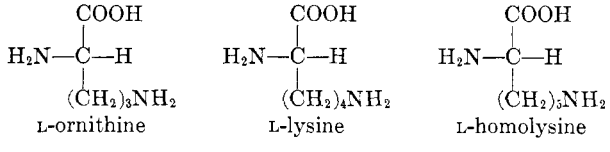
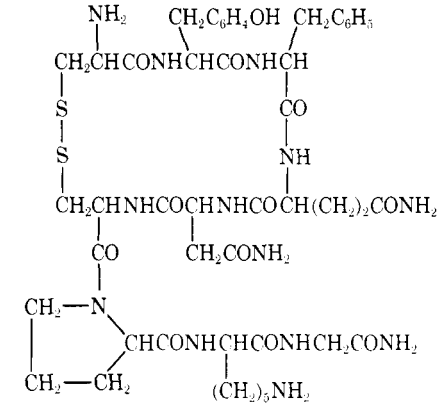
An analog of lysine-vasopressin in which the lysine residue was replaced by L-homolysine was synthesized stepwise by the nitrophenyl ester method. In the rat, the new hormone analog is a potent pressor and antidiuretic agent, both activities being comparable with those of the parent hormone.

The hormone analog 8-L-ornithine-vasopressin[3,4] is a potent pressor agent in the rat, but shows only a fraction of the antidiuretic activity of the parent hormone, lysine-vasopressin.[5] Thus the length of the side chain of the basic amino acid residue seems to play a significant role in the interaction between the hormone and the antidiuretic receptor site. The studies presented in this paper aimed at further exploration of the influence of this chain length. Since ornithine has a 3-C and lysine a 4-C side chain, it was decided to substitute the latter with L-homolysine (2,7-diaminoheptanoic acid) which has 5 C atoms in the corresponding part of the molecule.



The new hormone analog, 8-L-homolysine-vasopressin, was synthesized by the stepwise approach[6] with nitrophenyl esters[7] as acylating agents. The synthesis closely followed that of lysine-vasopressin,[8] except that the dipeptide and the tetrapeptide intermediates were not isolated in pure form and diisopropylethylamine[9] rather than Et_3N was used as the acid-binding agent in steps involving reactive derivatives of *S*-benzyl-L-cysteine. For the preparation of DL-homolysine, methods described in the literature[10–12] were applied, and resolution was performed on the diacetyl derivative with the aid of acylase.[13] The monoacetyl-L-homolysine obtained was deacetylated, then converted to the ζ-tosyl derivative *via* the copper complex, carbobenzoxylated on the α-amino group, and finally esterified with *p*-nitrophenol.[14] The active ester thus obtained was allowed to react with glycine ethyl ester,



8-L-homolysine-vasopressin

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