TABLE II
KNOWN COMPOUNDS

No.	Structure	Formula	LD50[a] Po	LD50[a] Ip	CNS[b] activity	Anti-inflammatory[c] activity	Endocrine effects[d] T	Th	C	B wt	L
25	$CF_3CH(OH)_2$	$C_2H_3F_3O_2$[7]	600	600	Depression	x	56	60	...	84	...
26	$CF_3CH(OH)(OCH_3)$	$C_3H_5F_3O_2$[5]	750	550	Depression	x	46	54	...	...	...
27	$CF_3CH(OH)(OC_2H_5)$	$C_4H_7F_3O_2$[5]	600	600	Depression	73	45	...	77	...	...
28	$CF_3CH(OC_2H_5)_2$	$C_6H_{11}F_3O_2$[5]	>1000	600	Depression	x	...	...	...	...	...
29	$C_2F_5CH(OH)_2$	$C_3H_3F_5O_2$[7]	600	600	Depression	x	...	...	...	...	...
30	$C_2F_5CH(OH)(OC_2H_5)$	$C_5H_7F_5O_2$[5]	1200	800	Depression	x	...	...	...	...	...
31	$CF_3(CF_2)_6CH(OH)_2$	$C_8H_3F_{15}O_2$[7]	>1000	>800	Depression	x	...	...	...	...	...
32	$CF_3CH(OCOCH_3)_2$	$C_6H_7F_3O_4$[8]	>1000	>1000		x	...	...	...	...	...

[a] The LD_{50} was determined in mice. [b] CNS effects were observed in normal mice. [c] Figures refer to the per cent reduction in edema, induced by carrageenin, relative to controls.[9] [d] Endocrine tests were performed on rats given 12 daily doses of 50 mg/kg subcut: T = testes; Th = thymus; C = cholesterol levels; B wt = body weight; L = liver; x = results not available; ... = not significantly different from controls. Figures refer to per cent wt relative to controls.

(50 ml). H_2O (1.8 g, 0.1 mole) was collected in a Dean–Stark trap in 2 hr. Excess C_6H_6 was removed by evapn and the residual oil was distd to give a colorless oil (5.0 g, 56%), bp 144–146°.

Method C. 2-Trifluoromethylimidazolidine (7).—Ethylenediamine (6.0 g, 0.1 mole) and trifluoroacetaldehyde hydrate (12 g, 0.104 mole) were refluxed in C_6H_6 (100 ml) for 2 hr. H_2O (2.5 ml) was collected in a Dean–Stark trap during this time. Solvent was removed by evapn under reduced pressure leaving an oil, which was dissolved in $CHCl_3$ and chromatographed on neutral Al_2O_3. Concn of the eluted material gave **7** as a white crystalline solid (11.8 g, 79%), mp 72–75°. Elemental analyses corresponded to a hemihydrate $C_4H_7F_3N_2 \cdot 0.5H_2O$, and this structure was supported by nmr and mass spectral measurements.

Method D. 2-Trifluoromethyl-4-ethyloxazolidine (11).—Trifluoroacetaldehyde hydrate (13.0 g, 0.11 mole) and 2-amino-1-butanol (8.9 g, 0.1 mole) in C_6H_6 (100 ml) were heated under reflux for 1.5 hr. A Dean–Stark trap was connected and the reaction was allowed to proceed until H_2O no longer collected in the trap. H_2O (3.6 g, 0.2 mole) was collected in 24 hr. C_6H_6 was removed by evapn under reduced pressure and the oily residue dissolved in $CHCl_3$ was purified by passage through a short neutral Al_2O_3 column. The purified solution was concd to give an oil which was distd to give a colorless oil (10.65 g, 63%), bp 148–153°.

Method E. Methyl 2-Trifluoromethyl-4,4-dimethylthiazolidine-5-carboxylate (18).—Trifluoroacetaldehyde hydrate (12 g, 0.104 mole) and penicillamine Me ester (16.3 g, 0.1 mole) in C_6H_6 (150 ml) were refluxed for 18 hr under a Dean–Stark trap. Solvent was removed by evapn to leave an oil which was distd to give a colorless oil (10.6 g, 44%), bp 68–72° (30 mm).

Method F. 1-Trifluoromethyl-4-ethyl-2,6,7-trioxabicyclo[2.2.2]octane (19).—Trifluoroacetic acid (12 g, 0.105 mole) and 2-ethyl-2-hydroxymethylpropane-1,3-diol (13.4 g, 0.1 mole) in *p*-xylene (100 ml) were refluxed together under a Dean–Stark trap for 6 hr. Xylene was removed by evaporation under reduced pressure and the residue in $CHCl_3$ was purified by passage through neutral Al_2O_3. The $CHCl_3$ soln was then concd to give a solid which was recrystd from petr ether (40–60°). Compd **19** was obtained as a white crystalline solid, mp 84° (15.0 g, 71%).

Acknowledgment.—We wish to express our appreciation to members of our Spectroscopy Laboratory for the determination of physicochemical properties and to many members of our Biology Department for carrying out the biological tests reported in this paper.

Perfluoroalkyl Carbonyl Compounds. 2. Derivatives of Hexafluoroacetone

GEORGE CRANK, DAVID R. K. HARDING, AND STEPHEN S. SZINAI*

Lilly Research Centre Limited, Erl Wood Manor, Windlesham, Surrey, England

Received January 16, 1970

Seventeeen derivatives of hexafluoroacetone (HFA), 9 of them novel compounds, have been synthesized and subjected to chemical and biological study. Some interesting chemical properties of these compounds are described. Significant activity against the parasite *Trypanosome rhodesiense* was found for HFA and some of its simple derivatives. It is suggested that HFA is the active agent, and that its derivatives owe their activity to the release of HFA *in situ*. Other biological activities were also observed.

Following our work on the perfluoroalkyl aldehydes[1] we now present a study of hexafluoroacetone. The objective was the examination of the biological properties of masked hexafluoroacetone (HFA), and as a consequence some simple derivatives of the ketone, with limited stability have been synthesised. The arguments presented in part 1[1] for this approach are also relevant to the present study.

The systems chosen for study were (a) $X(CH_2)_nYC(CF_3)_2$ where X or Y = O, S, NH and (b) $(CF_4)_2C(OH)R$ where R = N< or CH<

Chemistry.—The imidazolidines **1** and **2** (Table I) were prepared by the reaction of the diamine with hexafluoroacetone or with hexafluoroacetone sesquihydrate (HFAS). They were isolated as crystalline solids with 1 mole of H_2O firmly bound. This could not be removed by drying or by sublimation *in vacuo*. An nmr study of **1** showed that an equilibrium between the

* To whom correspondence should be addressed.

(1) G. Crank, D. R. K. Harding, and S. S. Szinai, *J. Med. Chem.*, **13**, 1212 (1970).

TABLE I: NOVEL COMPOUNDS

No.	Structure	Yield, %	Mp, °C	Formula	Analyses	LD$_{50}$[a] Oral	LD$_{50}$[a] Ip	Antitrypanosomal effect[b] Oral	Antitrypanosomal effect[b] Ip	Anti-inflammatory effect[c]	CNS effects[d]	Endocrine effects[e] T	Th	S.V.	B wt
1	$HNCH_2CH_2NHC(CF_3)_2 \cdot H_2O$	59	109–111	$C_5H_6F_6N_2 \cdot H_2O$	C, H, F, N	300	300	65	47	13	Depression and analgesia	60	56	63	88
2	$HNCH_2CH(CH_3)NHC(CF_3)_2 \cdot H_2O$	60	95–97	$C_6H_8F_6N_2 \cdot H_2O$	C, H, F, N	300	260	85	48	12	Depression	56	37	60	87
3	$HN(CH_2)_4C(CF_3)_2 \cdot H_2O$	36	108–112	$C_7H_{10}F_6N_2 \cdot H_2O$	C, H, F	300	290	83	35	38	Depression	x	x	x	x
4	$SCH_2CH_2NHC(CF_3)_2 \cdot H_2O \rightleftharpoons (CF_3)_2C(OH)NHCH_2CH_2SH$	51	115–117	$C_5H_5F_6NS \cdot H_2O$	C, H, F, N	300	300	39	44	11	Depression	69	37	72	78
5	$HNCH(CH_3)CH(C_6H_5)OC(CF_3)_2 \cdot H_2O \rightleftharpoons (CF_3)_2C(OH)NHCH(CH_3)CH(OH)C_6H_5$	35	116	$C_{12}H_{11}F_6NO \cdot H_2O$	C, H, N	200	300	25	37	0	Depression	x	x	x	x
6	$(CF_3)_2C(OH)NHCH_2CH_2OH$	61	107–109	$C_5H_7F_6NO_2$	C, H, N	330	330	0	0	0	Depression				
7	$(CF_3)_2C(OH)NHCH_2CH_2N(CH_3)_2$	93	97	$C_7H_{12}F_6N_2O$	C, H, F, N	330	330	32	43	16	Depression				
8	$(CF_3)_2C(OH)N(CH_2CH_2NH \cdot H_2O$	48	133–135	$C_7H_{10}F_6N_2O \cdot H_2O$	C, H, N	330	330	33	40	18	Depression				
9	$(CF_3)_2C(OH)NHAd \cdot 1.5H_2O$, Ad = 1-adamantyl	25	145–148	$C_{14}H_{19}F_6NO \cdot 1.5H_2O$	C, H, F, N	330	300	18	29		Depression				

[a] The LD$_{50}$ was determined in mice. [b] Compounds were tested against *Trypanosoma rhodesiense* infection in mice. Doses were 4 daily doses of 100 mg/kg by the oral route and 4 daily doses of 0.2 of the ip LD$_{50}$ by the ip route. Figures given refer to the per cent survival of the animals—controls have 0% survival. [c] The figures refer to the per cent reduction of edema produced by carrageenin relative to controls. Doses were 100 mg/kg (0.5 and 2 hr before carrageenin) in the rat. [d] CNS effects were observed in mouse behavior test. [e] 50 mg/kg per day given sc for 12 days to Wistar rats weighing 80 g: T = testes; S.V. = seminal vesicles; Th = thymus; B wt = body weight; % weight relative to controls; x = results not available; - = not significantly different from control.

two forms A and B existed, and that in polar solvents (D_2O, CD_3OD) the ring form A was predominant (>99%) whereas in nonpolar solvent (CCl_4) the open chain form B was predominant (>99%)

$$HNCH_2CH_2NHC(CF_3)_2 + H_2O \rightleftharpoons$$

A

$$(CF_3)_2C(OH)NHCH_2CH_2NH_2$$

B

Compounds **1**, **2**, and **3** were found to be stable in aq solutions between pH 1–9 for up to 24 hr. However, in the presence of electrophilic reagents they rapidly decomposed to HFA and substituted ethylenediamine, *e.g.*, acylation or alkylation caused this breakdown. Compounds **4** and **5** displayed similar properties but in these cases the equilibrium between the two structural forms contained appreciable amounts of both isomers. Compound **6** was present entirely in the noncyclic isomer.

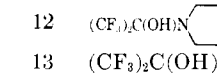
A few examples (**6**, **7**, **8**, **9**) of the structural type $(CF_3)_2{=}C(OH)(N<)$ were made by action of HFA on amines.[2] These compounds, while more stable than the cyclic compounds, were also reconverted into HFA fairly readily. In order to obtain more complete biological data we prepared some known derivatives of the type $(CF_3)_2{=}C(OH)(CH<)$ by reaction of HFA with the appropriate carbanion (pyridine as solvent).[2] It is an interesting feature of these compounds that when pyridine is used as solvent they are obtained as the pyridine complex. The required products were formed by treating the complexes with HCl.

Biological Activity.—The most interesting biological activity observed for the HFA derivatives was their effect on the parasitic infection caused by *Trypanosome rhodesiense*. The activity was highly specific for this particular organism, other species of trypanosomes being unaffected. From the pattern of activity it is considered that the compounds were acting by releasing HFA, which we postulate to be the active agent. For activity it seemed necessary to fulfil two conditions, (1) the derivatives of HFA must be fat-soluble, and, (2) the derivatives must not be too stable. HFAS was therefore submitted for testing and found to be significantly active when dosed by the ip route but barely active when given orally. This fact is probably due to HFAS being a highly polar molecule, which would be poorly absorbed orally and is therefore unlikely to reach the parasites. Most of our active derivatives, which show approximately equal activity by both dosage route, are fat-soluble molecules, and readily absorbed. Our hypothesis is further strengthened by the finding that some of the more chemically stable derivatives of HFA (**11**, **13**, **16**) were inactive. These compounds, although likely to be easily absorbed and transported are less likely to release HFA.

Other activities were also observed. Some members of the series showed moderate response on the anti-inflammatory screen. In rats, 12-day treatment with selected compounds caused marked reduction in growth rate suggesting some toxic effects and there was reduction in the size of certain endocrine organs.

(2) C. G. Krespan and W. J. Middleton, *Fluorine Chem. Rev.*, **1**, 145 (1967).

Table II
Known Compounds

No.	Structure	Formula	LD50[a] Oral	LD50[a] Ip	Antitrypanosomal effect[b] Oral	Antitrypanosomal effect[b] Ip	Anti-inflammatory effect[c]	CNS effects[d]	Endocrine effects[e] T	Th	S.V.	B wt
10	$(CF_3)_2C{=}O\cdot 1.5H_2O$	$C_3F_6O\cdot 1.5H_2O$[f]	300	250	5	55	21	Depression	81	77	53	88
11	$(CF_3)_2C(OCH_3)_2$	$C_5H_6F_6O_2$[g]	>800	>800	0	0		Depression	x	x	x	x
12		$C_8H_{11}F_6NO\cdot H_2O$[h]	300	300	37	40	0	Depression	...	...	...	...
13	$(CF_3)_2C(OH)CH(COOC_2H_5)_2$	$C_{10}H_{12}F_6O_5$[i]	1600	800	0	0	0	Mild depression	...	...	...	...
14	$(CF_3)_2C(OH)CH(COCH_3)COOC_2H_5$	$C_9H_{10}F_6O_4$[i]	800	500	68	66	0	Depression	...	...	...	...
15	$(CF_3)_2C(OH)CH(COCH_3)_2$	$C_8H_8F_6O_3$[i]	400	300	55	87	0	Depression	...	...	...	...
16	$(CF_3)_2C(OH)CH_2COOH$	$C_5H_4F_6O_3$[i]	1600	600	0	0	22	Depression	x	x	x	x
17	$(CF_3)_2CHOH$	$C_3H_2F_6O$[j]	600	300	0	0	0	Depression	x	x	x	x

[a] The LD_{50} was determined in mice. [b] Compounds were tested against *Trypanosoma rhodesiense* infection in mice. Doses were 4 daily doses of 100 mg/kg by the oral route and 4 daily doses of 0.2 of the ip LD_{50} by the ip route. Figures given refer to the per cent survival of the animals—controls have 0% survival. [c] The figures refer to the per cent reduction of edema produced by carrageenin relative to controls. Doses were 100 mg/kg (0.5 and 2 hr before carrageenin) in the rat. [d] CNS effects were observed in mouse behavior test. [e] 50 mg/kg per day given sc for 12 days to Wistar rats weighing 80 g: T = testes; S.V. = seminal vesicles; Th = thymus; B wt = body weight; % weight relative to controls; ... results not available; x not significantly different from control. [f] See ref 2. [g] J. J. Drysdale, U. S. Patent, 2,901,514 (1959); *Chem. Abstr.* **54,** 1320*f* (1960). [h] N. P. Gambaryan, E. M. Rokhlin, Yu, V. Ziefman, Cheng, Ching-Yun, and I. L. Knunyants, *Angew. Chem. Int. Ed. Engl.*, **5,** 947 (1966). [i] I. L. Knunyants, Tsin-Yun Chen, and N. P. Gambaryan, *V. Khim. Obshchest. D. I., M.*, **5,** 112 (1960); *Chem. Abstr.*, **54,** 20872*g* (1960). [j] I. K. Knunyants and M. P. Krasuskaya, U.S.S.R. Patent 138,604 (1960), *Chem. Abstr.*, **56,** 8563*g* (1962).

Experimental Section

Microanalytical figures for new compounds given in Table I agree with theoretical values to within 0.4%. The structures of all new compounds were confirmed by ir and nmr spectroscopy. Known compounds listed in Table II were prepared by established methods. Melting points are uncorrected and were measured in sealed capillary tubes. All compounds were prepared by similar methods, two representative preparations are given below.

2,2-Bis(trifluoromethyl)imidazolidine Monohydrate (1).—HFAS (5.8 g, 0.03 mole) and ethylenediamine (1.8 g, 0.03 mole) were mixed in C_6H_6 (150 ml). The mixture was refluxed for 0.5 hr, then for 6 hr under a Dean–Stark trap. During this period 1 ml of H_2O was collected. The C_6H_6 was removed by evapn leaving a white solid which was recrystd from Et_2O. The material was further purified by sublimation at 0.5 mm. The product, 4.0 g (59%), was a white crystalline solid, mp 109–111°.

2,2-Bis(trifluoromethyl)thiazolidine Monohydrate (4).—2-Mercaptoethylamine·HCl (10 g, 0.088 mole) in EtOH (100 ml) was deoxygenated by passage of dry N_2. The solution was neutralized by NaOEt. HFAS (17 g, 0.088 mole) was added and the mixture was boiled for 2 hr with passage of N_2. Solvent was removed and the residue was extracted with dry Et_2O. The ethereal extract was concd to give a crystalline solid, which was purified by recrystn from Et_2O. The product, 10.9 g (51%), was a white crystalline solid, mp 115–117°.

Acknowledgment.—We wish to express our appreciation to members of our Spectroscopy Laboratory for the determination of physicochemical properties and to many members of our Biology Department for carrying out the biological tests reported in this paper.

Structure–Taste Relationships of Aspartic Acid Amides

Robert H. Mazur,* Arthur H. Goldkamp, Patricia A. James, and James M. Schlatter

Chemical Research Department, G. D. Searle & Co., Skokie, Illinois 60076

Received January 12, 1970

It has been discovered that many α-amides of L-aspartic acid are sweet. The most potent products are derived from L-1-methyl-2-substituted-ethylamines where the substituent is Ph, cyclohexyl, *n*-Pr, *n*-Bu, or *i*-Bu.

During the synthesis of gastrin C-terminal tetrapeptide, tryptophylmethionylaspartylphenylalaninamide, one of us (J. M. S.) discovered that an intermediate, L-Asp-L-Phe Me ester, was intensely sweet.[1] Subsequent organoleptic evaluation has shown that the compound is 100–150 times as sweet as sucrose and free of unpleasant aftertaste.[2] Structural variations[1] in the Asp, Phe, and Me ester parts of the molecule were made. The presence of both the free, unsubstituted NH_2 and one CO_2H of Asp as well as the distance between them and the absolute configuration of the asymmetric C were completely critical for sweetness; the requirement of absolute L configuration also held for Phe. Sweetness fell off rapidly with increasing size of the ester radical. For example, the *n*-Pr ester had about 1% the potency of the Met ester. It was also found that Phe could be replaced by Met or Tyr to give dipeptide esters retaining substantial sweetening power.

At the present time the phenomenon of taste seems best explained by selective adsorption of chemical compounds onto a taste receptor.[3] The receptor is probably a site on the surface of a cell and is therefore a

* To whom correspondence should be addressed.

(1) R. H. Mazur, J. M. Schlatter, and A. H. Goldkamp, *J. Amer. Chem. Soc.*, **91,** 2684 (1969).

(2) R. H. Mazur, J. M. Schlatter, and L. Jokay, Program of the Institute of Food Technologists 29th Meeting, Chicago, Ill., May 1969, p 58.

(3) L. M. Beidler, *Advan. Chem. Ser.*, **56,** 1 (1966). We would like to thank a referee for calling our attention to Dr. Beidler's work.