We wish to thank Professor K. Venkatesan, Department of Organic Chemistry, Indian Institute of Science, Bangalore, for useful discussions and for suggesting the problem. We wish to thank Bangalore University for providing financial assistance.

References

BUERGER, M. J. (1959). *Vector Space and Its Applications in Crystal Structure Investigations*. New York: John Wiley.

CROMER, D. T. & WABER, J. T. (1965). *Acta Cryst.* **18**, 104–109.

GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* A**27**, 368–376.

GOVERDHAN MEHTA, GHOSH, P., CHAUDHURI, B., SINGH, V. K., USHA, R., VARUGHESE, K. I. & VENKATESAN, K. (1977). *Tetrahedron Lett.* **47**, 4109–4112.

SHELDRICK, G. M. (1976). *SHELX*. Program for crystal structure determination. Univ. of Cambridge, England.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

Acta Cryst. (1981). B**37**, 1790–1793

Fenfluramine Hydrochloride, (±)-*N*-Ethyl-*m*-(trifluoromethyl)amphetamine Hydrochloride*

BY GARY L. GRUNEWALD† AND MARY W. CREESE

Department of Medicinal Chemistry, The University of Kansas, Lawrence, Kansas 66045, *USA*

AND MICHAEL W. EXTINE

Molecular Structure Corporation, PO Box DF, College Station, Texas 77840, *USA*

(*Received* 22 *September* 1980; *accepted* 30 *March* 1981)

Abstract. $C_{12}H_{17}ClF_3N$, $M_r = 267{\cdot}72$, orthorhombic, *Pbca*, $Z = 8$, $a = 7{\cdot}302\ (1)$, $b = 26{\cdot}829\ (6)$, $c = 14{\cdot}366\ (2)$ Å, $D_c = 1{\cdot}264$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, μ(Cu $K\alpha$) = 2·57 mm^{-1}, $R = 0{\cdot}067$ for 705 observed reflections after anisotropic refinement of all non-H atoms. The solid-state conformations of the fenfluramine and amphetamine cations are the same.

Introduction. Single crystals of racemic fenfluramine hydrochloride were obtained by recrystallization from ethanol of a sample provided by A. H. Robins Co., Inc., Richmond, Virginia. A colourless prismatic crystal measuring 0·05 × 0·05 × 0·2 mm was used for the study. The symmetry was orthorhombic, and systematic absences were consistent with the space group *Pbca*. Intensity data were collected using an Enraf–Nonius CAD-4 diffractometer, a graphite monochromator, Cu $K\alpha$ radiation, and the θ–2θ scanning technique. Intensities were measured for 2513 independent reflections with $2\theta \leq 120°$. The intensity data were reduced to structure factors and corrected for Lorentz and polarization effects. No absorption or extinction corrections were necessary. The structure was determined by direct methods using *MULTAN* (Germain, Main & Woolfson, 1971), and refined by a full-matrix least-squares procedure. Anisotropic thermal parameters were used for the non-H atoms; the H atoms were fixed in calculated positions (C–H = 0·95 Å), with $B_{iso} = 8{\cdot}0$ Å^2, and not refined. The 705 reflections having $F_o^2 > 2\sigma(F_o^2)$ were used in the refinement. In the last cycle of refinement all parameter shifts were less than $0{\cdot}36\sigma$; $R = \sum||F_o| - |F_c||/\sum|F_o| = 0{\cdot}067$, and $R' = [\sum w(|F_o| - |F_c|)^2]^{1/2} = 0{\cdot}076$. The e.s.d. of an observation of unit weight was 1·549.

The molecular structure and the atom-numbering system are shown in Fig. 1. The final atomic coordinates are given in Table 1, and the bond lengths and angles in Tables 2 and 3 respectively.‡ The Enraf–Nonius structure-determination package was used for all the calculations.

Discussion. Fenfluramine produces some, but not all, of the pharmacological effects of amphetamine and related phenethylamines. Like the latter compounds it is effective as an appetite depressant (Le Douarec &

* Amphetamine is α-methylphenethylamine.

† To whom correspondence should be addressed.

‡ Lists of structure factors and thermal parameters and Table 4 have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36092 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

0567-7408/81/091790-04$01.00

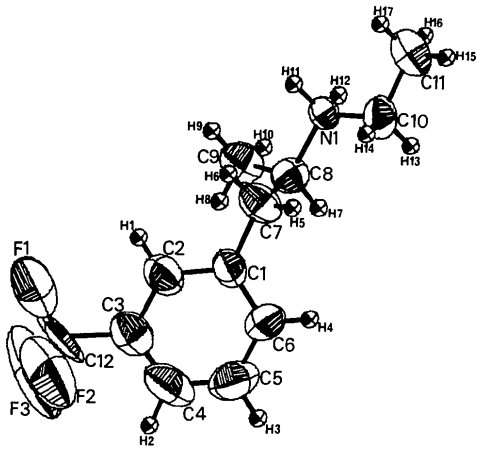

Fig. 1. Molecular structure and atom-numbering system of the title compound.

Table 1. *Positional parameters and equivalent isotropic thermal parameters with e.s.d.'s in parentheses*

$B_{eq} = \frac{1}{3}(B_{11} + B_{22} + B_{33})$.

	x	y	z	B_{eq} (Å^2)
C(1)	0·183 (1)	0·5905 (3)	0·3614 (7)	5·0 (5)
C(2)	0·290 (1)	0·5479 (3)	0·3686 (7)	6·6 (6)
C(3)	0·216 (2)	0·4996 (4)	0·3747 (6)	6·4 (6)
C(4)	0·031 (2)	0·4965 (4)	0·3742 (7)	8·3 (7)
C(5)	−0·079 (2)	0·5368 (4)	0·3672 (8)	8·2 (7)
C(6)	−0·006 (1)	0·5845 (3)	0·3616 (7)	5·9 (6)
C(7)	0·271 (1)	0·6404 (3)	0·3537 (6)	5·8 (5)
C(8)	0·233 (1)	0·6733 (3)	0·4382 (6)	4·8 (4)
C(9)	0·309 (1)	0·6526 (4)	0·5280 (7)	6·4 (6)
C(10)	0·236 (1)	0·7542 (4)	0·3468 (7)	5·7 (5)
C(11)	0·325 (1)	0·8037 (4)	0·3397 (8)	6·7 (6)
C(12)	0·337 (2)	0·4556 (3)	0·3938 (14)	15 (1)
N(1)	0·3148 (9)	0·7244 (2)	0·4239 (4)	3·5 (3)
F(1)	0·503 (1)	0·4649 (3)	0·3816 (9)	19 (1)
F(2)	0·325 (1)	0·4291 (3)	0·3045 (7)	16 (1)
F(3)	0·282 (1)	0·4240 (3)	0·4405 (7)	19 (1)
Cl(1)	0·7362 (3)	0·71125 (9)	0·3969 (2)	5·1 (1)
H(1)*	0·4191	0·5515	0·3695	
H(2)	−0·0243	0·4645	0·3790	
H(3)	−0·2086	0·5325	0·3662	
H(4)	−0·0837	0·6128	0·3578	
H(5)	0·2257	0·6566	0·2997	
H(6)	0·3998	0·6359	0·3480	
H(7)	0·1039	0·6746	0·4435	
H(8)	0·2898	0·6203	0·5387	
H(9)	0·4387	0·6505	0·5240	
H(10)	0·2763	0·6740	0·5781	
H(11)	0·4419	0·7204	0·4121	
H(12)	0·2984	0·7427	0·4799	
H(13)	0·1091	0·7587	0·3575	
H(14)	0·2538	0·7368	0·2899	
H(15)	0·2721	0·8219	0·2898	
H(16)	0·3078	0·8215	0·3963	
H(17)	0·4525	0·7995	0·3287	

* H-atom positions were calculated assuming idealized geometries and C–H = 0·95 Å.

Table 2. *Bond lengths* (Å) *with e.s.d.'s in parentheses*

C(1)–C(2)	1·387 (12)	C(7)–C(8)	1·526 (11)
C(1)–C(6)	1·387 (11)	C(8)–C(9)	1·509 (11)
C(1)–C(7)	1·489 (12)	C(10)–C(11)	1·482 (11)
C(2)–C(3)	1·404 (14)	C(12)–F(1)	1·25 (2)
C(3)–C(4)	1·357 (15)	C(12)–F(2)	1·47 (3)
C(3)–C(12)	1·50 (2)	C(12)–F(3)	1·15 (2)
C(4)–C(5)	1·351 (14)	N(1)–C(8)	1·509 (10)
C(5)–C(6)	1·393 (13)	N(1)–C(10)	1·482 (10)
Cl(1)–N(1)	3·121 (6)	Cl(1)–H(11)	2·173 (2)
Cl(1)′–N(1)	3·152 (6)	Cl(1)′–H(12)	2·206 (2)

Table 3. *Bond angles* (°) *with e.s.d.'s in parentheses*

C(8)–N(1)–C(10)	116·1 (6)	C(1)–C(7)–C(8)	112·5 (8)
C(2)–C(1)–C(6)	118·1 (1)	N(1)–C(8)–C(7)	110·3 (6)
C(2)–C(1)–C(7)	120·2 (9)	N(1)–C(8)–C(9)	107·8 (7)
C(6)–C(1)–C(7)	122·0 (1)	C(7)–C(8)–C(9)	113·7 (8)
C(1)–C(2)–C(3)	123·0 (1)	N(1)–C(10)–C(11)	111·5 (8)
C(2)–C(3)–C(4)	116·0 (1)	C(3)–C(12)–F(1)	113·0 (1)
C(2)–C(3)–C(12)	121·0 (1)	C(3)–C(12)–F(2)	101·0 (2)
C(4)–C(3)–C(12)	123·0 (2)	C(3)–C(12)–F(3)	119·0 (2)
C(3)–C(4)–C(5)	123·0 (1)	F(1)–C(12)–F(2)	92·0 (2)
C(4)–C(5)–C(6)	121·0 (1)	F(1)–C(12)–F(3)	125·0 (3)
C(1)–C(6)–C(5)	119·0 (1)	F(2)–C(12)–F(3)	98·0 (2)

Neveu, 1970; Elliot, 1970; Hadler, 1971; Hooper, 1972; Woodward, 1970), but its special interest lies in the fact that it does not produce several of the undesirable side effects associated with amphetamine therapy. For example, psychomotor stimulant effects are avoided and pressor activity is reduced (Le Douarec & Neveu, 1970; Bizzi, Bonaccorsi, Jespersen, Jori & Garattini, 1970; Spence & Medvei, 1966; Ziance, Sipes, Kinnard & Buckley, 1972), and recent animal studies indicate that addiction behaviour patterns common with amphetamines are not produced by fenfluramine (Woods & Tessel, 1974; Tessel & Rutledge, 1976; Tessel & Woods, 1975). The latter characteristic suggests that, in cases of amphetamine abuse by humans, fenfluramine could be a useful substitute.

Following from our interests in the conformational aspects of the activity of the adrenergic phenethylamines (Grunewald, Walters, Flynn, Atwood, Creese, Frenz & Troup, 1978; Grunewald, Reitz, Hallett, Rutledge, Vollmer, Archuleta & Ruth, 1980), we wondered whether a conformational difference, compared to amphetamine, might in part be responsible for the different pharmacological behaviour of fenfluramine. Hence we have compared the geometry of the molecule with that recently reported for amphetamine phosphate (Hebert, 1978).

Bond distances and valence angles (Tables 2 and 3) for the aromatic ring and the ethylamine side chain are close to expected values and in reasonable agreement with those recently reported for amphetamine phos-

Table 5. *Weighted least-squares planes and deviations (Å) of individual atoms*

The equations of the planes are in the form $Ax + By + Cz - D = 0$, where A, B, C, and D are constants, and x, y, and z are orthogonalized coordinates.

Since the weight given an atom depends on the error in its coordinates, the sum of the deviations will not necessarily be zero.

(1) Plane of benzene ring

$$0{\cdot}0129x - 0{\cdot}0759y - 0{\cdot}9970z - 6{\cdot}3656 = 0$$

C(1)	0·004 (10)	C(4)	−0·003 (11)
C(2)	−0·003 (10)	C(5)	0·005 (12)
C(3)	0·002 (9)	C(6)	−0·004 (10)

(2) Plane of side chain C(1)–N(1)

$$-0{\cdot}8438x + 0{\cdot}3277y - 0{\cdot}4250z + 1{\cdot}8295 = 0$$

C(1)	0·028 (9)	C(8)	−0·024 (9)
C(7)	−0·030 (10)	N(1)	0·012 (6)

(3) Plane of side chain C(9)–C(11)

$$0{\cdot}7321x - 0{\cdot}3846y - 0{\cdot}5622z - 9{\cdot}2652 = 0$$

C(9)	−0·081 (10)	C(10)	−0·053 (10)
C(8)	0·028 (9)	C(11)	−0·033 (11)
N(1)	0·050 (6)		

phate (Hebert, 1978) and 4-ethyl-2,5-dimethoxyamphetamine (Kennard, Giacovazzo, Horn, Mongiorgi & Riva di Sanseverino, 1974). Dihedral angles are as follows: C(6)–C(1)–C(7)–C(8) = 66 (1); C(1)–C(7)–C(8)–N(1) = −176·3 (6); C(7)–C(8)–N(1)–C(10) = 64·5 (8); C(8)–N(1)–C(10)–C(11) = 179·5 (7)°. Thus, the molecule may be thought of as three planes (see Table 5): (1) the plane of the benzene ring, (2) the plane of the ethylamine side chain, C(1)–C(7)–C(8)–N(1), and (3) the plane in which lie the atoms C(9), C(8), N(1), C(10) and C(11). Planes (1) and (2) form a dihedral angle of about 67°, and planes (2) and (3) form a dihedral angle of about 60°. Thus the ethylamine side chain is nearly fully extended and antiperiplanar as in amphetamine (Hebert, 1978; Bergin & Carlström, 1971). The methyl group, C(9), and the *N*-methyl group are oriented in the *trans* configuration.

A stereoscopic drawing of the molecular packing and the hydrogen-bonding system is shown in Fig. 2. Pertinent distances for the hydrogen bonds are given at the bottom of Table 2. The N atom is fully protonated, and the hydrogen bonds link N(1)–H(11)–Cl(1) and N(1)–H(12)–Cl(1)′ with N···Cl distances of 3·15 and 3·12 Å respectively. The sheets of fenfluramine cations lie along the *b* axis, and are held by the continuous network of hydrogen bonds which runs essentially perpendicular to **b** and which links their side chains. The aromatic rings are held by van der Waals forces only, and this may in part explain the large thermal motion (*cf.* Table 4)* of the trifluoromethyl

* See deposition footnote.

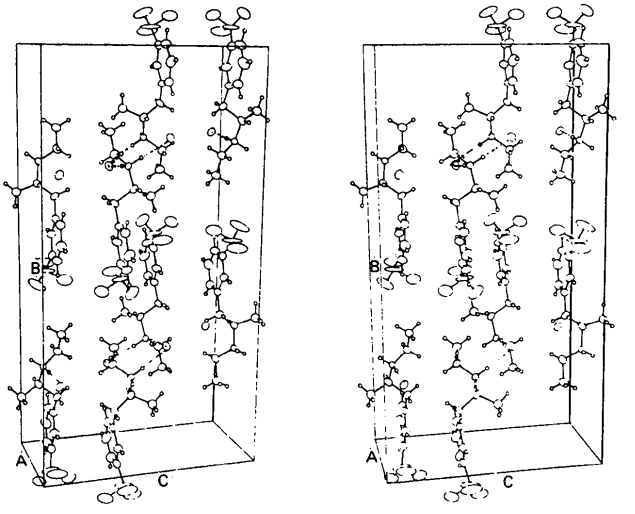

Fig. 2. Stereoscopic drawing of the molecular packing.

group. This hydrogen-bonded structure is quite similar to those previously observed in amphetamine sulphate (Bergin & Carlström, 1971) and in amphetamine phosphate (Hebert, 1978).

Thus the solid-state conformations of the fenfluramine and amphetamine cations are the same, with the side chains *trans* fully extended. This is consistent with our earlier observations in conformationally defined analogues of amphetamine (Grunewald *et al.*, 1978) for the requirement of a *trans* fully extended conformation for inhibition of re-uptake of norepinephrine into chopped brain tissue.

We acknowledge support of this work by research grant DA-01990 from the National Institute of Drug Abuse. Also we thank a referee for helpful comments about the hydrogen-bonding system.

References

BERGIN, R. & CARLSTRÖM, D. (1971). *Acta Cryst.* B**27**, 2146–2152.

BIZZI, A., BONACCORSI, A., JESPERSEN, S., JORI, A. & GARATTINI, S. (1970). *Amphetamines and Related Compounds*, edited by E. COSTA & S. GARATTINI, pp. 577–595. New York: Raven.

ELLIOT, B. W. (1970). *Curr. Ther. Res. Clin. Exp.* **12**, 502–515.

GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* A**27**, 368–376.

GRUNEWALD, G. L., REITZ, T. J., HALLETT, A., RUTLEDGE, C. O., VOLLMER, S., ARCHULETA, J. M. III & RUTH, J. A. (1980). *J. Med. Chem.* **23**, 614–620.

GRUNEWALD, G. L., WALTERS, D. E., FLYNN, D. L., ATWOOD, S. D., CREESE, M. W., FRENZ, B. A. & TROUP, J. M. (1978). *Acta Cryst.* B**34**, 3462–3465.

HADLER, A. J. (1971). *J. Clin. Pharmacol.* **11**, 52–55.
HEBERT, H. (1978). *Acta Cryst.* B**34**, 611–615.
HOOPER, A. C. B. (1972). *J. Ir. Med. Assoc.* **65**, 35–37.
KENNARD, O., GIACOVAZZO, C., HORN, A. S., MONGIORGI, R. & RIVA DI SANSEVERINO, L. (1974). *J. Chem. Soc. Perkin Trans.* 2, pp. 1160–1163.
LE DOUAREC, J. C. & NEVEU, C. (1970). *Amphetamines and Related Compounds*, edited by E. COSTA & S. GARATTINI, pp. 75–105. New York: Raven.
SPENCE, A. W. & MEDVEI, V. C. (1966). *Br. J. Clin. Pract.* **20**, 643–644.
TESSEL, R. E. & RUTLEDGE, C. O. (1976). *J. Pharmacol. Exp. Ther.* **197**, 253–262.
TESSEL, R. E. & WOODS, J. H. (1975). *Psychopharmacologia*, **43**, 239–244.
WOODS, J. H. & TESSEL, R. E. (1974). *Science*, **185**, 1067–1069.
WOODWARD, E. (1970). *Amphetamines and Related Compounds*, edited by E. COSTA & S. GARATTINI, pp. 685–691. New York: Raven.
ZIANCE, R. J., SIPES, I. G., KINNARD, W. J. JR & BUCKLEY, J. P. (1972). *J. Pharmacol. Exp. Ther.* **180**, 110–117.

Acta Cryst. (1981). B**37**, 1793–1796

Structure of 2,4,6-Tribromocholest-4-en-3-one

BY B. V. PRELESNIK AND R. M. HERAK

Laboratory of Solid State Physics and Radiation Chemistry, 'Boris Kidrič' Institute of Nuclear Sciences, PO Box 522, Yugoslavia

AND I. MIĆOVIĆ AND B. JELENKOVIĆ

University of Belgrade, Institute of Chemistry, PO Box 550, Belgrade, Yugoslavia

(*Received* 22 *May* 1980; *accepted* 31 *March* 1981)

Abstract. $C_{27}H_{41}Br_3O$, monoclinic, $P2_1$, a = 20·884 (4), b = 8·648 (2), c = 7·613 (2) Å, β = 92·57 (3)°, D_x = 1·502 Mg m^{-3} for Z = 2. The structure was solved by the heavy-atom method from 1728 four-circle X-ray diffractometer single-crystal data. The crystal structure was refined by the full-matrix least-squares method to a final R value of 0·083 (R_w = 0·076). The steroid rings A, B, C and D are *trans*-fused.

Introduction. The present work forms part of a stereochemical and synthetic investigation* of the dioxane dibromide (DBr_2) bromination of steroidal ketones.

Ambiguities in the interpretation of IR, UV, NMR and mass-spectral data, as well as the interpretation of ORD curves† for compounds (III) and (IV) (Fig. 1), prompted us to turn to X-ray crystallography for the positive identification of these structures. The present paper deals with the structure of the title compound (IV), whereas the crystal structure of (III) will appear later. The stereochemistry of the product (II) was assigned from its chemical correlation with compounds (III) and (IV).

Prismatic crystals of the steroid were grown by recrystallization from ethanol solution. Preliminary cell dimensions were obtained from Weissenberg and oscillation photographs using Cu $K\alpha$ (Ni-filtered) radiation. Systematic absences of $0k0$ reflexions for k odd were consistent with space group $P2_1$ (No. 4). A crystal of approximate dimensions 0·14 × 0·12 × 0·18 mm was used to collect the intensity data on a Philips PW 1100 single-crystal diffractometer using Mo $K\alpha$

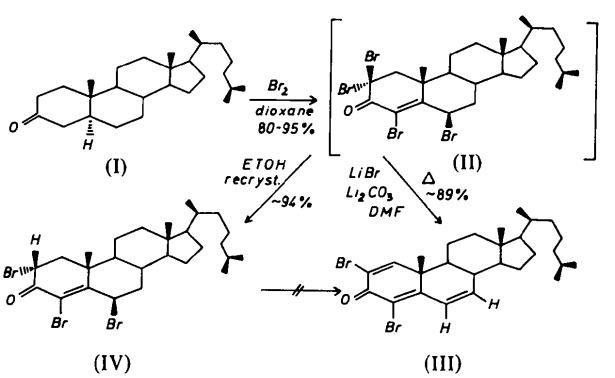

Fig. 1. The procedure for the isolation of 2,4,6-tribromocholest-4-en-3-one.

* Details of the synthesis and stereochemistry of polybrominated steroids will be published elsewhere (I. V. Mićović, to be published).

† We wish to express our appreciation to Professor Dr G. Snatzke, Ruhr-Universität Bochum, for interpretations of the ORD curves.

0567-7408/81/091793-04$01.00