Fluorination of Trichlormethiazide with Fluoroxytrifluoromethane

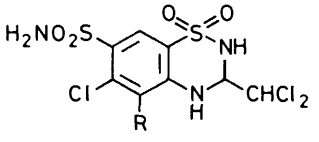
By **Derek H. R. Barton, Robert H. Hesse,* Maurice M. Pechet,** and **Hee T. Toh,** Research Institute for Medicine and Chemistry, Cambridge, Massachusetts 02142, U.S.A.

Reaction of trichlormethiazide (1; R = H) with fluoroxytrifluoromethane yields the diaziridine (2), the 5-fluoro-derivative (1; R = F), and the 4*H*-1,2,4-benzo[*e*]thiadiazine 1,1-dioxide (4). The reaction is influenced by the amount of hydrogen fluoride present, and possibly proceeds *via* the *N*-fluoro-derivative (5).

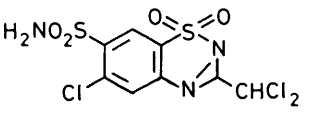
We have previously shown that perfluorofluoroxy-compounds are mild and efficient reagents for the specific synthesis of a variety of *C*- and *N*-fluoro-compounds.[1] We now report on the reaction of fluoroxytrifluoromethane with trichlormethiazide (6-chloro-3-dichloromethyl-7-sulphamoyl-3,4-dihydro-2*H*-1,2,4-benzo[*e*]thiadiazine 1,1-dioxide) (1; R = H). Trichlormethiazide, a diuretic and antihypertensive drug,[2] is representative of a number of biologically important compounds based on the 7-sulphamoyl-1,2,4-benzo[*e*]thiadiazine 1,1-dioxide nucleus.[2,3] These compounds contain a range of functional groups with potential reactivity towards electrophilic fluorination.

RESULTS AND DISCUSSION

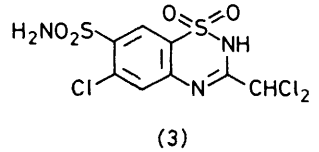
Treatment of trichlormethiazide with fluoroxytrifluoromethane gave three products, (2), (1; R = F), and (4). Compound (2) was isolated by chromatography on an alumina column. Material from a separate experiment was then chromatographed on silica gel to yield (1; R = F) and (4).



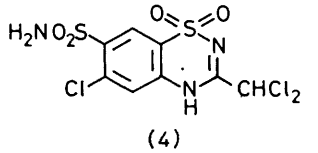
(1)



(2)



(3)



(4)

Compound (1; R = F) analysed for the substitution of one hydrogen of trichlormethiazide by fluorine. Comparison of the ^{1}H n.m.r. spectra of (1; R = H) and (1; R = F) (see Table 1) indicated the structure. In confirmation, the ^{19}F n.m.r. spectrum consisted of an overlapping double doublet at +128.5 p.p.m. ($J_{F,C-8H}$ and $J_{F,N-4H}$ each 2 Hz) which collapsed to a doublet on shaking with deuterium oxide.

The molecular formula of (2) was established as $C_8H_6Cl_3N_3O_4S_2$. Mass spectroscopy showed that it exchanged two hydrogens with deuterium oxide under the same conditions that caused trichlormethiazide to exchange four hydrogens. The u.v. spectra of starting material and product showed considerable differences (see Experimental section). The significant feature of the n.m.r. spectrum of (2) was the considerable upfield shift of the C-3 and dichloromethyl protons relative to their positions in compounds (1; R = H and F). Such shielding is typical of that observed for protons associated with a three-membered ring,[4] and in conjunction with the other spectroscopic data suggested the diaziridine structure (2). In keeping with this, reduction of (2) with aqueous potassium iodide or zinc regenerated trichlormethiazide (1; R = H).

TABLE 1

^{1}H N.m.r. data for trichlormethiazide and derivatives

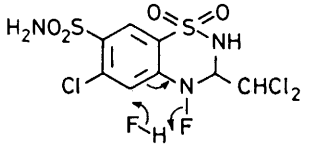
Compound	Chemical shift (multiplicity and coupling constants in parentheses) *						
	N-2-H	C-3-H	$CHCl_2$	N-4-H	C-5-H	C-8-H	SO_2NH_2
Trichlormethiazide (1; R = H)	7.5 (br s)	5.4 (d, 5)	6.5 (d, 5)	3.1 (br s)	7.3 (s)	8.2 (s)	6.8 (br s)
(2)		4.6 (d, 6)	6.1 (d, 6)		8.0 (s)	8.5 (s)	7.0 (br s)
(1; R = F)	7.4 (br s)	5.5 (d, 5)	6.6 (d, 5)	2.9 (br s)		8.1 (d, 2)	6.9 (br s)
(4)			6.9 (s)	11 (br s)	7.6 (s)	8.2 (s)	7.8 (br s)

* Chemical shifts in p.p.m., coupling constants in Hz.

On heating *slowly* to 100 °C the diaziridine (2) was converted quantitatively into (4). Significant amounts of the same product were also formed when the diaziridine (2) was stored at room temperature for periods of about one month. The absence in the n.m.r. spectrum of a signal for the C-3-H and the appearance of the dichloromethyl proton as a singlet at δ 6.9 indicated structure (3) or (4) for this product. It has been shown that for such compounds the 4*H*-isomer is the more stable,[3,5] and we therefore favour structure (4) for our product.

Whilst various mechanisms can be written to explain the formation of the above three products, an attractive possibility involves the *N*-fluoro-derivative (5) as a common intermediate. Alternative modes of elimination of hydrogen fluoride would yield the diaziridine (2) or the 2*H*-1,2,4-benzo[*e*]thiadiazine 1,1-dioxide (3), the latter then rearranging to the 4*H*-isomer (4). Particip-

ation of hydrogen fluoride [(5), see arrows] could account for the transfer of fluorine to C-5 and hence formation of (1; R = F). Evidence in support of this possibility was provided by the effect of adding extra hydrogen fluoride or removing the hydrogen fluoride generated



(5)

during the reaction using calcium oxide (see Table 2). Control experiments using sulphuric acid or trifluoroacetic acid indicated that these effects were not simply a reflection of changes in acidity. An analogous process is the rearrangement of *N*-chloroanilines into *o*- and *p*-chloroanilines.[6]

TABLE 2

Reaction of trichlormethiazide with fluoroxytrifluoromethane under various conditions

Reaction medium	(2)	% Yields (1; R = F)	(4)
20% Acetone–methylene chloride	25	24	20
20% Acetone–methylene chloride + calcium oxide	40	12	
20% Acetone–methylene chloride–hydrogen fluoride	10 *	36	
20% Acetone–methylene chloride–trifluoroacetic acid	10 *	20	
Tetrahydrofuran–hydrogen fluoride		50	
Methanol–sulphuric acid	10 *	20	70
Methanol	25 *	20	55

* Estimated by t.l.c.

EXPERIMENTAL

General directions are as previously stated.[1d] Trichlormethiazide has $\lambda_{max.}$ 225, 267, and 313 nm (ε 47 400, 22 600, and 2 800).

Fluorination of Trichlormethiazide (1; R = H).—Calcium oxide (700 mg) was added to trichlormethiazide (760 mg, 2 mmol) in acetone (10 ml) and methylene chloride (40 ml). The solution was cooled to 0 °C and fluoroxytrifluoromethane undiluted with nitrogen was slowly bubbled through. When no starting material remained (t.l.c.) the calcium was filtered off, and the filtrate evaporated. T.l.c. indicated the presence of three products. The least polar product (2) could be detected by spraying the chromatogram with aqueous potassium iodide. Chromatography on grade II neutral alumina, eluting with 20% acetone–methylene chloride afforded the *diaziridine* (2), m.p. (from acetone–hexane) 325—328 °C (decomp.) [this is the m.p. of (4) formed by thermal rearrangement]; $\nu_{max.}$ 3 500, 3 400, 1 590, 1 370, 1 360, 1 350, 1 180, and 955 cm^{-1}; $\lambda_{max.}$ 221 and 250 nm (ε 36 200 and 8 170); *m/e* 377, 379, 381, and 383 (M^+), molecular weight 370 (osmometry) (Found: C, 25.55; H, 1.7; Cl, 28.0; N, 10.9; S, 16.7. $C_8H_6Cl_3N_3O_4S_2$ requires C, 25.4; H, 1.6; Cl, 28.1; N, 11.1; S, 16.9%). Further elution with acetone gave no material corresponding to (1, R = F) or (4). The experiment was repeated and the product chromatographed on silica. The first compound eluted was *5-fluorotrichlormethiazide* (1; R = F), m.p. (from acetone–hexane) 250—253 °C; $\nu_{max.}$ 3 480, 3 350, 3 300, 1 600, 1 345, 1 165, 1 150, and 780 cm^{-1}; δ_F([$^2H_6$]acetone) +128.5 (dd, *J* 2 and 2 Hz, d after exchange with deuterium oxide); $\lambda_{max.}$ 223, 264, and 310 nm (ε 44 500, 14 100, and 3 700) (Found: C, 24.5; H, 2.0; Cl, 26.8; F, 4.8; N, 10.6; S, 15.9. $C_8H_7Cl_3FN_3O_4S_2$ requires C, 24.1; H, 1.8; Cl, 26.7; F, 4.8; N, 10.5; S, 16.1%). Further elution gave the *4H-1,2,4-benzo[e]thiadiazine 1,1-dioxide* (4), m.p. (from acetone–hexane) 325—328 °C (decomp.); $\nu_{max.}$ 3 500, 3 350, 1 615, 1 600, 1 580, 1 525, 1 370, 1 350, 1 330, 1 300, 1 170, and 970 cm^{-1}; $\lambda_{max.}$ 213, 305, and 323 nm (ε 37 500, 11 400, and 13 800) (Found: C, 25.5; H, 1.9; Cl, 27.8; N, 10.8; S, 16.8. $C_8H_6Cl_3N_3O_4S_2$ requires C, 25.4; H, 1.6; Cl, 28.1; N, 11.1; S, 16.9%). The results of analogous experiments using different solvent mixtures are summarised in Table 2.

Reduction of the Diaziridine (2).—(*a*) The diaziridine (50 mg) and zinc dust (200 mg) in acetone were stirred at room temperature until the solution gave a negative test with potassium iodide–starch paper (10 min). The mixture was filtered and the filtrate evaporated to give trichlormethiazide, identical with an authentic sample.

(*b*) The diaziridine (20 mg) in acetone was treated with aqueous potassium iodide at room temperature for 20 min. Iodine was removed by the addition of aqueous sodium thiosulphate. The mixture was extracted with ethyl acetate to yield, after p.l.c., trichlormethiazide (15 mg).

Pyrolysis of the Diaziridine (2).—The diariridine (50 mg) was heated *slowly* in an open test tube. After 1 h at 80 °C only starting material remained. After similar periods at 90 and 100 °C conversion into the *4H*-1,2,4-benzo[*e*]thiadiazine 1,1-dioxide (4) was 20 and 100% complete, respectively.

[9/712 *Received*, 9*th May*, 1979]

REFERENCES

[1] (*a*) D. H. R. Barton, R. H. Hesse, M. M. Pechet, G. Tarzia, H. T. Toh, and N. D. Westcott, *Chem. Comm.*, 1972, 122; (*b*) D. H. R. Barton, R. H. Hesse, H. T. Toh, and M. M. Pechet, *J. Org. Chem.*, 1972, **37**, 329; (*c*) D. H. R. Barton, R. H. Hesse, L. Ogunkoya, N. D. Westcott, and M. M. Pechet, *J.C.S. Perkin I*, 1972, 2889; (*d*) D. H. R. Barton, R. H. Hesse, M. M. Pechet, and H. T. Toh, *J.C.S. Perkin I*, 1974, 732; (*e*) J. Leroy, F. Dudragne, J. C. Adenis, and C. Michaud, *Tetrahedron Letters*, 1973, 2771.

[2] ' United States Dispensatory,' ed. A. Osol, R. Pratt, and M. D. Altschule, Lippincott, Philadelphia, 26th edition, 1967, p. 1199.

[3] F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, 1960, **25**, 970.

[4] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, 2nd edn., p. 98.

[5] A. J. Wohl, ' Drug Design,' ed. A. J. Ariens, Academic Press, New York, 1971, vol. I, p. 390.

[6] P. G. Gassman, E. Campbell, and R. Frederick, *J. Amer. Chem. Soc.*, 1968, **90**, 7377; D. F. Paul and P. Haberfield, *J. Org. Chem.*, 1976, **41**, 3170.