4-Amino-2-perfluoroalkyl-5-halomethylpyrimidines[1]

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The preparation and biological activity of a 2-trifluoromethyl analog of thiamin ("trifluorothiamin," XII) were described in a recent paper.[3] In order to improve the preparation of this analog and to synthesize the 2-pentafluoroethyl (XIII) and 2 - heptafluoro - *n* - propyl (XIV) analogs, a simpler method for the preparation of the intermediate 4-amino-2-perfluoroalkyl-5-halomethylpyrimidines was considered necessary.

It was found that the reaction of nitrous acid with the corresponding 4-amino-5-aminomethyl-2-perfluoroalkylpyrimidines in the presence of a high concentration of chloride or bromide ion mitigated this difficulty. 5 - Halomethylpyrimidines were formed readily with the more nucleophilic bromide ion giving the better yields. 2-Heptafluoro-*n*-propyl-5-iodomethylpyrimidine was obtained by a similar procedure but in low yield due to the competing reduction of nitrous acid by iodide ion. The reaction is not reported in the experimental.

The effective use of this preparative method for halomethyl compounds apparently requires: (1) compounds which do not undergo rearrangement by a carbonium ion mechanism; (2) products which precipitate from the medium at the *p*H necessary for diazotization; (3) reactions where large amounts of halide ion can be used to favor the preparation of a halomethyl compound over solvolysis. Preliminary work indicated that the method seemed satisfactory for the preparation of benzyl bromide from benzylamine but not for the preparation of 4-amino-5-bromomethyl-2-methylpyrimidine from 4-amino-5-aminomethyl-2-methylpyrimidine which contains a basic 4-amino group. The basicity of the 4-amino group of the 2-perfluoroalkylpyrimidines is reduced by the electron-withdrawing effect of the 2-perfluoroalkyl groups and therefore precipitation of the desired product occurs.

4 - Amino - 5 - aminomethyl - 2 - pentafluoroethylpyrimidine (IV) and 4 - amino - 5 - aminomethyl - 2 - heptafluoro - *n* - propylpyrimidine (V) were prepared by the method reported earlier[4] for 4-amino - 5 - aminomethyl - 2-trifluoromethylpyrimidine (III).

The chloromethyl and bromomethylpyrimidines were converted to the corresponding 2-perfluoroalkyl analogs of thiamin by a modification of the method of Williams and Cline.[5] Compounds XII, XIII, and XIV were oxidized[6] with alkaline potassium ferricyanide according to the method of Barger, Bergel, and Todd.[7] Although the quantities of the products obtained under the conditions used were insufficient for identification, fluorescence, which could be interpreted as showing the presence of thiocrome-type derivatives, was qualitatively observed in the chloroform solutions in each case.

The infrared spectra[8] for XII prepared from the chloromethyl compound by the method referred to in this paper was identical with that of XII prepared by method B of our previous paper,[3] involving closure of the thiazole ring. A comparison of the spectrograms for thiamin (Sadtler[9]-No. 324) and compounds XII, XIII, and XIV showed many similarities. The most significant difference was due to the strong absorption bands between 1275 and 1100 cm.$^{-1}$, which were present in the fluorinated analogs but not in thiamin. These bands were attributed to the carbon-fluorine bonds of the trifluoromethyl and difluoromethylene groups. This strong absorption was also present in those spectrograms (Nos. 15255–15264) obtained by Sadtler[9] from certain 2-trifluoromethylpyrimidines, the preparations of which were previously described.[4]

The biological activities of the compounds prepared are being studied and will be reported elsewhere.

EXPERIMENTAL[10]

4-Amino-5-cyano-2-pentafluoroethylpyrimidine (I) *and 4-amino-5-cyano-2-heptafluoro-n-propylpyrimidine* (II). Compounds I and II were prepared from 2-pentafluoropropionamidine[11a,b] and heptafluoro-*n*-butyramidine[11a,b] according to the method for 4-amino-5-cyano-2-trifluoromethylpyrimidine reported previously,[4] but, in the case of II, a 3-hr. reflux was necessary. The analytical samples were obtained by recrystallizing twice from methanol.

4-Amino-5-aminomethyl-2-trifluoromethylpyrimidine (III), *4-amino-5-aminomethyl-2-pentafluoroethylpyrimidine* (IV), *and 4-amino-5-aminomethyl-2-heptafluoro-n-propylpyrimidine* (V). These compounds[12] were prepared from the respective

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(3) J. A. Barone, H. Tieckelmann, R. Guthrie, and J. F. Holland, *J. Org. Chem.*, 25, 211 (1960).

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(5) R. R. Williams and J. K. Cline, *J. Am. Chem. Soc.*, 58, 1504 (1936).

(6) The technical assistance of Mr. John Bognar with the oxidations is gratefully acknowledged.

(7) G. Barger, F. Bergel, and A. R. Todd, *Ber.*, 68, 2257 (1935).

(8) Infrared spectra on the thiamin analogs were obtained by Mr. Frank Bajer using KBr pellets.

(9) *Catalog of Infrared Spectrograms*, Samuel P. Sadtler and Son, Philadelphia.

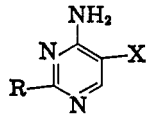
(10) Microanalyses by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected. Those reported to be the same for the thiamin analogs were run simultaneously because the rate of heating did cause variance.

(11) (a) D. Husted, U. S. Patent 2,676,985 (April 1954). (b) W. L. Reilly and Henry C. Brown, *J. Am. Chem. Soc.*, 78, 6032 (1956).

(12) The technical assistance of Miss Arlyn Meininghaus with the hydrogenations is gratefully acknowledged.

TABLE I

4-AMINO-2-PERFLUOROALKYLPYRIMIDINES



Compound	R	X	Yield, %	M.P.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	CF_3CF_2	CN	69	177–179	35.31	1.27	—	35.34	1.28	—
II	$CF_3CF_2CF_2$	CN	62	148–149	33.35	1.05	—	33.24	1.21	—
IV	CF_3CF_2	CH_2NH_2	80	134–135	34.71	2.91	—	34.90	3.13	—
V	$CF_3CF_2CF_2$	CH_2NH_2	71	90.5–92.5	32.88	2.36	—	32.54	2.10	—
VI	CF_3	CH_2Cl	54	191–192	[a]	—	—	—	—	—
VII	CF_3CF_2	CH_2Cl	47	134–136	32.14	1.93	16.06	32.57	2.23	15.95
VIII	$CF_3CF_2CF_2$	CH_2Cl	54	110–112	30.83	1.62	13.49	30.60	1.87	13.51
IX	CF_3	CH_2Br	60	186–188	28.14	1.97	16.44	28.29	1.85	16.41
X	CF_3CF_2	CH_2Br	72	145–146.5	27.47	1.65	13.73	27.53	1.44	13.79
XI	$CF_3CF_2CF_2$	CH_2Br	78	131–133.5	26.98	1.42	11.80	27.10	1.29	12.04

[a] Identified by comparison with an authentic sample.[3]

TABLE II

2-PERFLUOROALKYL ANALOGS OF THIAMIN

No.	Compound	M.P.	% Yield from 5-CH_2Cl	% Yield from 5-CH_2Br	Calcd. C	Calcd. H	Calcd. Cl	Found C	Found H	Found Cl
XII	$C_{12}H_{15}Cl_2F_3N_4OS \cdot H_2O$	192.5–194.5	75[a]	88[a]	[b]	—	—	—	—	—
XIII	$C_{13}H_{15}Cl_2F_5N_4OS \cdot H_2O$	193–195	60	77	33.99	3.73	15.44	34.03	3.71	15.73
XIV	$C_{14}H_{15}Cl_2F_7N_4OS \cdot H_2O$	179.5–182	43	61	33.01	3.37	13.93	33.19	3.43	14.14

[a] Reaction temperatures were 135–140° and 145–150° respectively. For the other reactions, a temperature of approximately 155° was used. [b] Identified by comparison with an authentic sample.[3]

5-cyano compounds in the manner previously reported for III.[4] For the purification of V and part of IV, a benzene-ethanol solution was treated with ethanol–hydrogen chloride and precipitated salt was dissolved in water, filtered, and converted to the free amine with 10% aqueous sodium hydroxide.

4-Amino-5-chloromethyl-2-trifluoromethylpyrimidine (VI), *4-amino-5-chloromethyl-2-pentafluoroethylpyrimidine* (VII), *and 4-amino-5-chloromethyl-2-heptafluoro-n-propylpyrimidine* (VIII). Four grams (0.0208 mole) of III was dissolved in a solution of 3.4 ml. (0.042 mole) of concd. hydrochloric acid in 20 ml. of water. This was combined with a solution of 48.7 g. (0.832 mole) of sodium chloride in 140 ml. of water, filtered, and heated to 60°. Then 1.66 g. (0.0243 mole) of sodium nitrite in 12 ml. of water was added dropwise with stirring. A voluminous white precipitate formed almost immediately. The mixture was cooled in an ice water bath and filtered. The precipitate was dried on a porous plate and then in a vacuum desiccator. The product was dissolved in acetone-benzene and filtered. The solution was concentrated, cooled, and filtered to give 2.37 g. as a first crop. A second crop of 0.23 g., m.p. 163–174°, was not included in the yield in Table I. A portion of the first crop was recrystallized from acetone-benzene to give a sample which had the same melting point as the analytical sample of VI described in our previous paper,[3] and a mixed melting point showed no depression. The omission of sodium chloride gave a mixture of VI, 4-amino-2-trifluoromethyl-5-hydroxymethylpyrimidine (identified by comparison with an authentic sample[4]), and 2-trifluoromethyl-4-hydroxy-5-hydroxymethylpyrimidine. The analytical sample of the last compound, m.p. 166–167.5°, was obtained by recrystallizing twice from ethanol-benzene.

Anal. Calcd. for $C_6H_5F_3N_2O_2$: C, 37.72; H, 2.60; N, 14.42. Found: C, 37.46; H, 2.81; N, 14.40.

VII was obtained in a similar manner using 3.14 g. (0.0130 mole) of IV, 30.4 g. (0.520 mole) of sodium chloride, 2.1 ml. (0.026 mole) of concd. hydrochloric acid and sodium nitrite and water in the proportional amounts used for VI. The analytical sample was obtained by recrystallization from benzene.

VIII was also prepared by this method using 3.04 g. (0.0104 mole) of V, 24.3 g. (0.416 mole) of sodium chloride and the other reagents in the proportional amounts used for VI. Inorganic matter was removed by extracting with ether, filtering, and evaporating the ether to give the reported product. The analytical sample was obtained by recrystallizing twice from benzene.

4-Amino-5-bromomethyl-2-trifluoromethylpyrimidine (IX), *4-amino-5-bromomethyl-2-pentafluoroethylpyrimidine* (X), *and 4-amino-5-bromomethyl-2-heptafluoro-n-propylpyrimidine* (XI). Compounds IX, X, and XI were obtained from 4.00 g. samples of the corresponding amines, III, IV, and V, in the manner and concentrations reported for the 5-chloromethyl compounds except that 48% hydrobromic acid and sodium bromide (40 times the amine concentration) were used. A preliminary experiment for the preparation of IX on a smaller scale indicated that lowering the sodium bromide concentration to 25 times that of the amine resulted in a lower yield. Increasing it to 60 times gave a slightly better yield for IX and a slightly lower yield for X. This latter concentration could not be obtained in the preparation of XI because of the appearance of a heavy precipitate.

3-[(4-Amino-2-perfluoroalkyl-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium chloride hydrochlorides. The 2-trifluoromethyl (XII), 2-pentafluoroethyl (XIII), and 2-heptafluoro-*n*-propyl (XIV) analogs of thiamin were prepared by the method of Williams and Cline[5] as modified by Stein,[13] *et al.* A mixture of 0.0047 mole of the crude

5-halomethylpyrimidine, 0.0070 mole of 5-(2-hydroxyethyl)-4-methylthiazole,[14] and 5 ml. of light paraffin oil was used. The reaction products were isolated essentially by the method reported earlier for XII.[3] The products from the 5-bromomethylpyrimidines gave negative bromide tests and were used for the analytical samples after purification by dissolving in ethanol and adding ethanol–hydrogen chloride. These samples had the same melting points as those obtained from the respective 5-chloromethylpyrimidines and the mixed melting points showed no depression.

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(13) G. A. Stein, *et al.*, *J. Am. Chem. Soc.*, **63**, 2059 (1941).

(14) The authors are grateful to Dr. Max Tishler and Dr. Anthony H. Land, Merck Sharp and Dohme Research Laboratories, for a sample of this compound.

Alkyl- and Arylthiomethylpiperazines

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In continuation of our research in the field of piperazine chemistry, we have prepared a series of alkyl- and arylthiomethylpiperazines. Analogous compounds have been prepared by others[3–5] by condensing secondary amines with formaldehyde and a thiol using anhydrous potassium carbonate to absorb the water formed. In preparing this series, we have used minor modifications of the methods used by these investigators.

$$R_2NH + HCHO + R'SH \longrightarrow R_2CH_2SR' + H_2O$$

Utilization of an arenethiol in this reaction could theoretically lead to compounds of this same chemical class or to Mannich bases of the type produced with phenols, but Grillot and coworkers[5] have shown that aryldialkylaminomethyl sulfides are ordinarily formed. Our findings have confirmed their results.

A total of forty-eight compounds were prepared, using ethane-, butane-, benzene-, and *p*-toluenethiols and a series of twelve piperazines. Physical data on these compounds are compiled in Tables I and II. The compounds have been submitted to Parke, Davis and Co. for pharmacological screening.

EXPERIMENTAL

Preparation of alkyl- and arylthiomethylpiperazines. The thiol was added dropwise with stirring to an equivalent

(1) Deceased.

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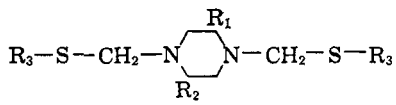
TABLE I

ALKYLTHIOMETHYLPIPERAZINES



R_1	R_2	R_3	B.P. or M.P.[a]	Yield, %	n_D^{25}	Analyses[b] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
H—	H—	C_2H_5—	140–141(0.30)	40	1.5314	51.24	51.60	9.46	9.28
H—	CH_3—	C_2H_5—	126–126.5 (0.40)	32	1.5283	53.18	53.42	9.74	9.61
CH_3—	CH_3—	C_2H_5—	57.1–58.8	49		54.91	54.72	9.99	9.98
H—	H—	*n*-C_4H_9—	43.5–46.6	52		57.89	57.90	10.41	10.05
H—	CH_3—	*n*-C_4H_9—	157–158 (0.075)	54	1.5157	59.14	59.11	10.59	10.34
CH_3—	CH_3—	*n*-C_4H_9—	32.4–34.5	48		60.33	60.42	10.76	10.62
H—	H—	C_6H_5—	100–102.9	55		65.42	65.70	6.71	7.01
H—	CH_3—	C_6H_5—	43.5–46.6	52		66.23	66.18	7.02	7.12
CH_3—	CH_3—	C_6H_5—	97.0–98.0	48		67.00	67.10	7.31	7.21
H—	H—	*p*-CH_3—C_6H_4—	127.3–130.4	84		67.00	67.30	7.31	7.68
H—	CH_3—	*p*-CH_3—C_6H_4—	68.7–70.8	69		67.72	67.45	7.58	7.55
CH_3—	CH_3—	*p*-CH_3—C_6H_4—	135.3–137.4	62		68.35	68.36	7.82	7.78

[a] Figure in parentheses represents pressure (mm.) at which distillation was carried out and all melting points are corrected.
[b] Analyses for N% and S% also checked.