TABLE I

TRIALKYL ARYLTHIOMETHYLAMMONIUM IODIDES AND PICRATES

Cation	Melting Point, °C.	Iodide Analysis % Carbon Calcd.	Iodide Analysis % Carbon Found	Iodide Analysis % Hydrogen Calcd.	Iodide Analysis % Hydrogen Found	Picrate Melting Point °C.	Picrate Analysis % Carbon Calcd.	Picrate Analysis % Carbon Found	Picrate Analysis % Hydrogen Calcd.	Picrate Analysis % Hydrogen Found
Phenylthiomethyl triethylammonium	150.4–152.2[a,b]					121–122.4	50.43	50.71	5.35	5.52
Ethyl phenylthiomethyl piperidinium	oil					90.6–92	51.72	52.05	5.21	5.40
Ethyl phenylthiomethyl morpholinium	oil					102.6–104	48.92	48.79	4.75	4.88
Ethyl *p*-chlorophenylthiomethyl morpholinium	oil					133–135	45.56	45.42	4.23	4.34
Ethyl *p*-chlorophenylthiomethyl piperidinium	oil[c]					131.4–133	48.14	48.33	4.65	4.80
Phenylthiomethyl triethylammonium	152.4–154[a,d]	38.84	39.09	5.216	5.363	126–127.6	46.82	46.96	4.42	4.74
p-Chlorophenylthiomethyl triethylammonium	155–156[d,e]	40.47	40.35	5.488	5.338	103.8–105	46.86	47.40	4.76	4.94

Picrates recrystallized from ethyl alcohol. Carbon and hydrogen analysis performed by Drs. Weiler and Strauss, 164 Banbury Road, Oxford, England.

[a] Recrystallized from ethyl acetate. [b] Yield about 25%. [c] Yield about 28% based on yield of crude sample. [d] Recrystallized from ethyl acetate–chloroform mixture. [e] Yield about 20%.

47%. Bordwell and Pitt[4] reported a boiling point of 103–104°/12 mm.

Benzyl phenylthiomethyl dimethylammonium chloride was obtained by the action of *N*,*N*-dimethylbenzylamine on phenyl chloromethyl sulfide according to the procedure of Barber *et al.*[4] The crude product was obtained in a yield of 84% and melted at 164–170°. After recrystallization from a chloroform-ethyl acetate mixture, it melted at 168–171°. The melting point previously reported was 161–165°.[4] The picrate melted at 125–126°, (literature; 124–125°).

Method B. Dimethylaminomethyl phenyl sulfide was prepared by adding dropwise 20.5 ml. (0.2 mole) of thiophenol to 13 ml. (0.2 mole) of cold dimethylamine and then adding to the resulting mixture 18 g. (0.2 mole) of formalin. This reaction mixture was heated at 80° for 2 hr. and after cooling was extracted with ether. The ether extract was dried over anhydrous $MgSO_4$. After removal of the ether, a fraction boiling at 112–116°/9–11 mm. was obtained in a yield of 23.8 g. or 71%.

Benzyl phenylthiomethyl dimethylammonium chloride was then prepared by following the general method described by Wagner and Zook.[9,10]

To a solution of 8.4 g. (0.05 mole) of dimethylaminomethyl phenyl sulfide in 20 ml. of benzene was added 5.8 ml. (6.33 g.; 0.05 mole) of benzyl chloride. After standing for 17 hr. 3 g. of material separated. If the mother liquor was heated for 4 hr. at 60° an additional 2.7 g. of the product precipitated giving combined a yield of 40%. After two recrystallizations from a chloroform-ethyl acetate mixture it melted at 170.2–171° and gave no depression of the melting point when mixed with the quaternary ammonium salt prepared by Barber's method.

This chloride salt was converted to the picrate which melted at 124.8–125.4° and gave no depression of the melting point when mixed with the picrate obtained by the method of Barber.

Trialkyl phenylthiomethylammonium iodides. General method. The dialkylaminomethyl aryl sulfide, prepared by the method previously described by Grillot *et al.*,[1] was dissolved in a small volume of benzene and to this solution was added an equivalent quantity of ethyl or methyl iodide. If a crystalline precipitate did not form at once, the reaction mixture was heated at 60° until either a crystalline product or an oily residue formed. Although many of these compounds were oils that would not crystallize, all could be converted to crystalline picrates. Melting points, solvents for recrystallization, and analytical data for the crystalline iodides and picrates obtained are detailed in Table I.

CHEMISTRY DEPARTMENT
SYRACUSE UNIVERSITY
SYRACUSE, 10, N. Y.

(9) R. B. Wagner and H. D. Zook, *Synthetic Organic Chemistry*, Method 436, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 668.

(10) R. S. Shelton, M. G. Van Campen, C. H. Tilford, H. C. Lang, L. Nisonger, F. J. Bandelin, and H. L. Rubenkoenig, *J. Am. Chem. Soc.*, 68, 753, 755, 757 (1946).

Synthesis of Potential Anticancer Agents. V. Convenient Synthesis of 4(5)-Amino-5(4)-carboxamido-1,2,3-triazole[1]

L. L. BENNETT, JR. AND HARRY T. BAKER

Received December 17, 1956

The ribotide of 4-amino-5-imidazolecarboxamide (AIC) has been implicated for some time as an intermediate in biosynthesis of purines.[2] Since many of the agents that temporarily inhibit growth of

(1) This work was supported by a grant from the American Cancer Society. For the preceding paper in this series, see ref. 4.

(2) See, among others, (a) G. R. Greenberg, *Federation Proc.*, 13, 745 (1954). (b) M. P. Schulman and J. M. Buchanan, *J. Biol. Chem.*, 196, 513 (1954).

neoplasms are known to inhibit purine synthesis,[3] analogs of AIC are of interest as potential anticancer agents. As part of a study of compounds which might interfere with the imidazole intermediates in biosynthesis of purines,[4] the 1,2,3-triazole analog of AIC and some related compounds were prepared. While this paper was in preparation, Hoover and Day[5] reported the preparation of 4(5)-amino-5(4)-carboxamido-1,2,3-triazole and a number of other triazoles. However, our method of preparation of this analog of AIC was different from theirs and is of some interest in that this method apparently has not been employed hitherto in the triazole series.

The success of Taylor and co-workers[6,7] in preparing a number of 3-amino-5,6-diphenylpyrazinamides by the aminolytic cleavage of 6,7-diphenyllumazine suggested that this method might be applied conveniently to the preparation of 4(5)-amino-5(4)-carboxamido-1,2,3-triazole from 8-azaxanthine. It was found that this triazole could be obtained in good yield when 8-azaxanthine[8,9] was heated with ammonium hydroxide essentially under the conditions used by Taylor[6] for the conversion of 6,7-diphenyllumazine to 3-amino-5,6-diphenylpyrazinamide. Acetylation of the triazole gave a diacetyl derivative which showed the lability toward water characteristic of some other ring-acylated nitrogen heterocycles[10] and readily lost one acetyl group to give 4(5)-acetamido-5(4)-carboxamido-1,2,3-triazole.

By other methods, two phenyl derivatives of this triazole were also prepared as potential antagonists of AIC. When phenylazide and cyanoacetamide were allowed to react under conditions commonly used for synthesis of triazoles from azides and active methylene compounds,[5,11,12] 1-phenyl-4-carboxamido-5-amino-1,2,3-triazole was obtained in high yield. This compound, when heated with pyridine, underwent rearrangement to a product that, by analogy with rearrangements reported for a number of triazoles of similar structure,[12] was formulated as 4(5)-carboxamido-5(4)-phenylamino-1,2,3-triazole. The esters corresponding to both of these triazole carboxamides are known compounds,[12] but attempts to prepare the amides from the esters were unsuccessful.

(3) H. E. Skipper, *Cancer Research*, **13**, 545 (1953).
(4) L. L. Bennett and H. T. Baker, *J. Am. Chem. Soc.*, **79**, 2188 (1957).
(5) J. R. E. Hoover and A. R. Day, *J. Am. Chem. Soc.*, **78**, 5832 (1956).
(6) E. C. Taylor, *J. Am. Chem. Soc.*, **74**, 1651 (1952).
(7) E. C. Taylor, J. A. Carbon, and D. R. Hoff, *J. Am. Chem. Soc.*, **75**, 1904 (1953).
(8) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole, and J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **67**, 290 (1945).
(9) L. F. Cavalieri, A. Bendich, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, **70**, 3875 (1948).
(10) H. A. Staab, *Chem. Ber.*, **89**, 1927 (1956).
(11) O. Dimroth, *Ber.*, **35**, 4041 (1902).
(12) O. Dimroth, *Ann.*, **364**, 183 (1909).

EXPERIMENTAL[13]

4(5)-Amino-5(4)-carboxamido-1,2,3-triazole. 8-Azaxanthine[9] (5.0 g.) and 200 ml. of concentrated ammonium hydroxide were placed in a small steel bomb. While the bomb was rocked, the temperature was raised to 195–200° (about 1 hr. required) and then kept at 175–185° for 4 hr. At the end of this time the bomb was cooled rapidly to room temperature and opened, after which the clear amber liquid, which rapidly darkened on standing, was transferred to a flask. The triazole was precipitated as the silver salt which was washed thoroughly with water, then suspended in water, and finally decomposed with hydrogen sulfide. The filtrate resulting from removal of silver sulfide was concentrated to dryness *in vacuo* leaving an almost colorless residue. Crystallization from water gave 2.3 g. of colorless crystals, m.p. 223.5–224.0°; reported,[5] 224–225°. Concentration of the mother liquor gave a second crop of 0.59 g., a total yield of 70%. A sample for analysis was recrystallized several times from water and dried at 56° *in vacuo*.

Anal. Calcd. for $C_3H_5N_5O$: C, 28.35; H, 3.97; N, 55.10. Found: C, 28.33; H, 4.15; N, 55.22.

Spectral Data. λ_{max} in mμ (a_M): pH 7–226 (9.71×10^3), 261 (9.74×10^3); pH 10–266 (9.84×10^3). $\bar{\nu}$ in cm.$^{-1}$: 1625 (primary amino group); 1660 (amide carbonyl). The ultraviolet spectrum at pH 7 agrees well with that reported[5] in 50% ethanol.

For preparation of the diacetyl derivative 0.10 g. of the compound was dissolved in a boiling solution of 3 ml. of acetic anhydride and 0.5 ml. of acetic acid. After being boiled for 5 min., the solution was cooled and the white precipitate which resulted was washed with alcohol and ether; wt. 0.12 g., m.p. 210–212°.

Anal. Calcd. for $C_7H_9N_5O_3$: C, 39.81; H, 4.30; N, 33.17. Found: C, 39.62; H, 3.98; N, 33.10.

The infrared spectrum showed strong absorption at 1735 cm.$^{-1}$ and a shoulder at 1715 cm.$^{-1}$; heterocycles containing a ring *N*-acyl group are known to absorb in this region.[14] This compound was therefore formulated as 4(5)-acetamido-5(4)-carboxamido-1,2,3-triazole with a second acetyl group on one of the ring nitrogen atoms.

When the diacetyl derivative (0.055 g.) was boiled for 5 min. in 3 ml. of water, crystals began to separate from the hot solution. After the solution had been cooled, the solid was separated and washed with cold water. The colorless product weighed 0.035 g. (79%), melted at 267–268°, and analyzed as a monoacetyl derivative. The infrared spectrum showed that absorption in the range 1700–1750 cm.$^{-1}$, characteristic of the ring acyl group, had been destroyed by the treatment with water.

Anal. Calcd. for $C_5H_7N_5O_2$: C, 35.50; H, 4.17. Found: C, 35.55; H, 4.40.

1-Phenyl-4-carboxamido-5-amino-1,2,3-triazole. This compound was prepared essentially by the method used by Dimroth[12] for the synthesis of 1-phenyl-4-carbethoxy-5-amino-1,2,3-triazole, except that cyanoacetamide was used in place of ethyl cyanoacetate.

To a solution of cyanoacetamide (5.65 g.) in 150 ml. of absolute ethanol there were added in succession a sodium ethylate solution (prepared from 42 ml. of absolute ethanol and 1.5 g. of sodium) and 8.0 g. of phenyl azide. There was an immediate precipitation of solid and the mixture became sufficiently hot to require cooling. After a few minutes, the solid redissolved. After the amber solution had been allowed to stand for three days, the voluminous solid was collected and washed with ethanol; wt. 12.0 g. (87%). For preparation of an analytical sample, a portion was recrystallized once from water and three times from ethanol. The product melted at 162–163°; the melt solidified at 165–167° and the

(13) Melting points are uncorrected. Infrared spectra were run in pressed potassium bromide pellets with a Perkin-Elmer Model 21 spectrophotometer.
(14) W. Otting, *Chem. Ber.*, **89**, 1940 (1956).

solid then melted again at about 200°. The melting points varied with the duration of heating. This behavior is probably due to thermal rearrangement which has been reported[12] to occur in related triazoles.

Anal. Calcd. for $C_9H_9N_5O$: C, 53.19; H, 4.46; N, 34.47. Found: C, 52.94; H, 4.32; N, 34.32.

Spectral Data. λ_{max} in mμ (a_M) in absolute alcohol: 225 (10.2×10^3), 253 (shoulder) (9.50×10^3). The spectrum was similar to that of 1-phenyl-4-carbethoxy-5-amino-1,2,3-triazole, prepared according to Dimroth.[12]

4(5)-Carboxamido-5(4)-phenylamino-1,2,3-triazole. For rearrangement of 1-phenyl-4-carboxamido-5-amino-1,2,3-triazole, the conditions used were those reported by Dimroth[12] for the rearrangement of 1-phenyl-4-carbethoxy-5-amino-1,2,3-triazole to 4(5)-carbethoxy-5(4)-phenylamino-1,2,3-triazole. After the 1-phenyl derivative had been refluxed in pyridine for 3 hr., the reaction mixture was cooled and neutralized with hydrochloric or acetic acid to precipitate the triazole. The triazole, thus obtained in 75% yield, melted at 200–201° after being recrystallized from absolute ethanol. The elemental analysis was the same as that of the starting material. The ultraviolet absorption spectrum, determined in absolute ethanol, had maxima at 262 mμ (a_M, 10.2×10^3) and at 297 mμ (a_M, 9.93×10^3) and was similar to that found for 4(5)-carbethoxy-5(4)-phenylamino-1,2,3-triazole.[12]

Acknowledgments. The authors wish to thank Drs. Glynn P. Wheeler and John A. Montgomery for helpful suggestions; Mr. J. P. Holmquist for elemental analyses; and Dr. W. C. Coburn and Mr. J. W. Murphy for infrared spectra determinations.

KETTERING-MEYER LABORATORY[15]
SOUTHERN RESEARCH INSTITUTE
BIRMINGHAM, ALA.

(15) Affiliated with Sloan-Kettering Institute.

New Trifluoromethylphenothiazine Derivatives

PAUL N. CRAIG, EDWARD A. NODIFF, JOHN J. LAFFERTY, AND GLENN E. ULLYOT

Received January 22, 1957

We wish to make a preliminary report of some physical and chemical data on aminoalkyl fluorine-substituted phenothiazines with pronounced pharmacological activity.[1,4] Phenothiazine drugs containing halogen or methoxyl substituents have been discussed by Viaud.[2] Smith has reported several trifluoromethylphenothiazines,[3] but no 10-aminoalkyl derivatives thereof have been described chemically. A preliminary report on the pharmacological activity of compounds 2 and 9 (Table III) has been presented.[4a,b] A brief clinical report[4c] on the antiemetic and psychotherapeutic effectiveness of com-

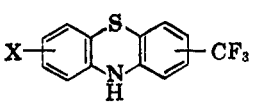
(1) The pharmacology of these drugs will be published in detail elsewhere by Dr. Leonard Cook and coworkers of these laboratories.

(2) P. Viaud, *J. Pharm. Pharmacol.*, **6**, 361 (1954).

(3) N. L. Smith, *J. Org. Chem.*, **15**, 1125 (1950).

(4) (a) J. C. Burke, H. L. Yale, G. L. Hassert, Jr., and J. P. High, Program, The American Society for Pharmacology and Experimental Therapeutics Meeting, French Lick, Ind., Nov. 8–10, 1956, p. 11. (b) J. J. Piala, J. P. High, K. Greenspan, and J. C. Burke, Program, The American Society for Pharmacology and Experimental Therapeutics Meeting, French Lick, Ind., Nov. 8–10, 1956, p. 11. (c) P. K. Conner, W. Fraser, S. I. Kinard, H. Bennett, and J. H. Moyer, *Clin. Res. Proc.*, **5** (1), 121 (1957).

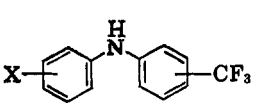
TABLE I



X	CF_3 (Position)	M.P., °C.[a]	Yield, %	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H[b]	4	71–72°	5	$C_{13}H_8F_3NS$	58.42	3.02	5.24	58.54	3.18	5.38
8-Cl	2	188–189°	8.5	$C_{13}H_7ClF_3NS$	51.75	2.34		52.10	2.59	
7-OCH_3	2	169–170°	19	$C_{14}H_{10}F_3NOS$	56.56	3.39	4.71	56.63	3.62	4.75

[a] Uncorrected. [b] Prepared by H. E. Reiff and J. Jaffe of these (SKF) Laboratories.

TABLE II



X	CF_3 (Position)	B.P., °C.	Yield, %	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3-Cl	3′	128–9°/0.05 mm.	57	$C_{13}H_9ClF_3N$	57.47	3.34	5.16	57.41	3.37	5.26
4-OCH_3	3′	m.p. 59–60°	41	$C_{14}H_{12}F_3NO$	62.92	4.53	5.24	63.00	4.65	5.16