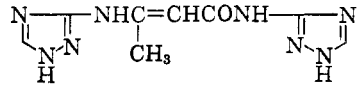
TABLE II

AMINE SALTS OF VARIOUS TETRAZAINDENES

Amine	Tetraza-indene	M.P.	Mol. Wt.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	λ_{max} ($\epsilon \times 10^{-3}$) at pH ~1	λ_{max} ($\epsilon \times 10^{-3}$) at pH ~10
n-Propylamine	I	165[a]	209	51.7	7.2	33.5	51.5	7.2	32.9	270 (11.1)	255 (6.3) 280 (11.7)
Diethylamine	I	160	223	53.4	7.6	31.4	53.3	7.4	31.8	270 (11.6)	255 (6.6) 280 (12.3)
Triethylamine	XII	138–140	309	54.2	7.4	—	54.0	7.2	—	282 (11.3) 247 (8.7)	293 (15.6) 262 (9.4)
Hydrazine	I	178–180	182	39.6	5.5	46.1	40.4	5.4	47.7	270 (11.8)	255 (6.8) 280 (12.4)
3-Amino-1,2,4-triazole[b]	I		234							270 (11.0)	255 (6.3) 280 (11.6)
3-Amino-5-methyl-1,2,4-triazole	[c]	238–240	278	43.2	5.0	40.4	43.2	5.0	40.8	270 (10.6)	255 (6.3) 280 (11.6)
3,5-Dimethylpiperidine	I	160	263	59.4	8.0	26.6	59.8	8.0	26.7	270 (11.3)	255 (6.4) 280 (12.0)
Morpholine	I	160	237	50.7	6.3	29.5	50.6	6.4	30.0	270 (11.1)	255 (6.4) 280 (11.9)

[a] M.p. 169–170° after recrystallization from benzene. [b] This salt was previously given the erroneous structure[6]:



[c] 2-Hydroxymethyl derivative of I (ref. 8, p. 745).

Acknowledgment. The authors are indebted to Mrs. E. M. Gordon for ultraviolet spectra, to Dr. D. W. Stewart and Miss T. J. Davis for infrared spectra, and to Dr. E. P. Przybylowicz for sublimation of the salt, III. The helpful interest and advice of Dr. C. F. H. Allen are acknowledged with gratitude.

ROCHESTER 4, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ARIZONA STATE UNIVERSITY]

Purine Nucleosides. II. The Preparation of 6-Substituted 9-(Tetrahydro-2-furyl)purines and 6-Substituted 9-(Tetrahydro-2-thienyl)purines as Models of Purine Deoxynucleosides[1,2]

LELAND R. LEWIS, F. HOWARD SCHNEIDER, AND ROLAND K. ROBINS

Received February 27, 1961

The reaction of 2,3-dihydrofuran or 2,3-dihydrothiophene with certain 6-substituted purines in the presence of acid has been shown to yield the corresponding 9-(tetrahydro-2-furyl)- or 9-(tetrahydro-2-thienyl)purine. This reaction provides a novel method of introducing a five-membered ring into position 9 of the purine ring. These derivatives are interesting models of purine deoxynucleosides, several of which possess significant antitumor activity against adenocarcinoma 755. As there are no hydroxyl groups present for *in vivo* phosphorylation, these compounds are interesting candidates for further biochemical study at the nucleoside level. The synthesis of 9-(tetrahydro-2-furyl)adenine (III), a model of deoxyadenosine, has been accomplished from 6-chloro-9-(tetrahydro-2-furyl)purine (I).

A program of synthesis of various purine derivatives as antitumor agents revealed that certain 9-alkyl-6-substituted purines such as 9-methyl-6-purinethiol[3] and 9-methyl-6-chloropurine[3] retained a considerable amount of the antitumor activity possessed by the parent 6-substituted purines. As the corresponding 7-methyl-6-purinethiol[4] and 7-methyl-6-chloropurine[4] were devoid of antitumor activity, it seemed possible that the 9-substituted purines might owe their activity to the structural relationship to purine nucleosides rather than to possible *in vivo* demethylation. As 6-chloro-9-phenylpurine[5] and 9-phenyl-6-purinethiol[5] exhibited no antitumor activity, an effort was made

(1) Supported by Contract SA-43-ph-1928 with the Cancer Chemotherapy National Service Center of the National Cancer Institute, National Institutes of Health.

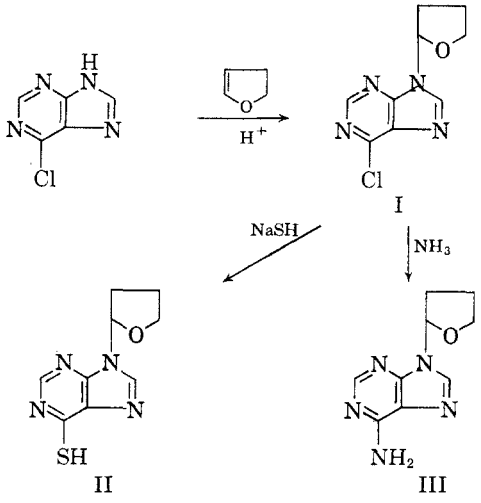
(2) Presented in part before the Division of Organic Chemistry at the 138th Meeting of the American Chemical Society, September 1960, New York, N. Y.

(3) R. K. Robins and H. H. Lin, *J. Am. Chem. Soc.*, 79, 490 (1957).

(4) R. N. Prasad and R. K. Robins, *J. Am. Chem. Soc.*, 79, 6401 (1957).

(5) S. M. Greenberg, L. O. Ross, and R. K. Robins, *J. Org. Chem.*, 24, 1314 (1959).

to substitute the planar phenyl ring by the tetrahydropyran ring system which would more closely resemble the natural purine nucleoside. Synthesis of various 9-(tetrahydro-2-pyranyl)purines[6] has revealed that these derivatives also exhibit significant tumor inhibition. As the naturally occurring purine nucleosides are known to possess the furanoside structure, the present work was undertaken to introduce the tetrahydrofuran ring at position 9.



REACTION SCHEME I

The reaction of 2,3-dihydrofuran[7] with 6-chloropurine[8] in the presence of a catalytic amount of acid readily provided 6-chloro-9-(tetrahydro-2-furyl)purine (I) in excellent yield. Transformation of I to 9-(tetrahydro-2-furyl)-6-purinethiol (II) was readily accomplished with methanolic sodium hydrosulfide. The preparation of 9-(tetrahydro-2-furyl)adenine (III) from I proceeded at room temperature with methanolic ammonia. Aqueous dimethylamine and I provided 6-dimethylamino-9-(tetrahydro-2-furyl)purine. Reaction of I with ethanolamine in methanol similarly provided smooth nucleophilic replacement of the chlorine atom to provide 6-(β-hydroxyethylamino)-9-(tetrahydro-2-furyl)purine. When 2,3-dihydrofuran was treated directly with other 6-substituted purines, it was found that 6-iodopurine,[9] 6-cyanopurine,[10] 6-bromopurine,[9] 6-methylthiopurine,[11] and other 6-substituted thiopurines readily provided the corresponding 9-(tetrahydro-2-furyl)-6-substituted purine derivatives.

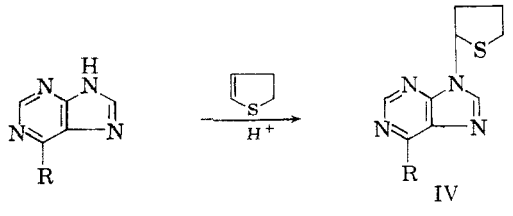
(6) R. K. Robins, E. F. Godefroi, E. C. Taylor, L. R. Lewis, and A. Jackson, *J. Am. Chem. Soc.*, **83**, 2574 (1961).
(7) R. Paul, *Bull. soc. chim. France*, 668 (1950).
(8) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).
(9) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 3508 (1956).
(10) L. B. Mackay and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 3511 (1958).
(11) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952).

The assignment of the location of the tetrahydro-2-furyl group to position 9 is based on a comparison of the ultraviolet absorption spectra of a number of 9-(tetrahydro-2-furyl)-6-substituted purines with the corresponding 7- and 9-methylpurine derivatives (see Table I). 6-Chloro-9-(tetrahydro-2-furyl) purine in ethanol exhibits a maximum at 266 mμ (ε 9000) similar to 6-chloro-9-methylpurine with a maximum at 265 mμ (ε 9100) while 6-chloro-7-methyl purine possesses a maximum at 271 mμ (ε 7300). The absorption spectra of 6-methylthio-9-(tetrahydro-2-furyl)purine also support assignment to position 9 since both 6-methylthio-9-(tetrahydro-2-furyl)purine and 9-methyl-6-methylthiopurine in ethanol exhibit maxima at 284 mμ in contrast to the maximum of the 7-methyl-6-methylthiopurine at 293 mμ.

Baker, Schaub, and Joseph[12] report absorption maxima for 6-dimethylamino-9-methylpurine at 270 and 277 mμ at a *p*H of 1 and 14, respectively, and for the 6-dimethylamino-7-methylpurine, 290 and 295 mμ at a *p*H of 1 and 14, respectively. 6-Dimethylamino-9-(tetrahydro-2-furyl)purine exhibits maxima at 275 and 277 mμ at a *p*H of 1 and 12, respectively. The ultraviolet absorption spectra of the corresponding adenine derivatives give added support to assignment to position 9, as the 9-tetrahydro-2-furyl derivative (III) in ethanol possesses a maximum at 261 mμ similar to 9-methyladenine, maximum at 262 mμ, while that of 7-methyladenine is 272 mμ in ethanol.

The ultraviolet absorption spectra of the 9-(tetrahydro-2-furyl)purines prepared are listed in Table II. The ease of introduction of the tetrahydrofuran group and the ready availability of 2,3-dihydrothiophene[13] suggested the extension of the reaction to the preparation of some 9-(tetrahydro-2-thienyl)purines (IV), which would also possess a five-membered ring of similar structure.

Although the reaction did not proceed as readily as with 2,3-dihydrofuran, when an excess of 2,3-dihydrothiophene and an extended reaction period was employed, the desired product (IV) was obtained. A study of the



R = Cl, Br, I, SCH_3

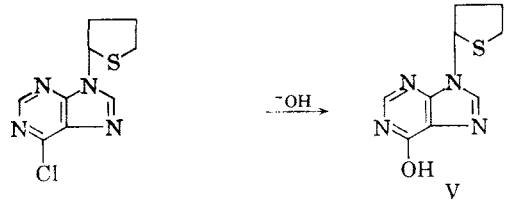
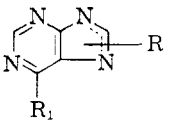


TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF SOME 9-(TETRAHYDRO-2-FURYL)- AND 9-(TETRAHYDRO-2-THIENYL)-6-SUBSTITUTED PURINES AND RELATED 7- AND 9-METHYLPURINES[a]

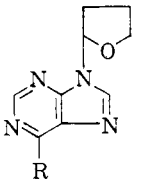


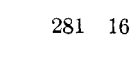
	7-Methyl[4]		9-Methyl[3]		9-(Tetrahydro-2-furyl)		9-(Tetrahydro-2-thienyl)	
R_1	mμ	ε	mμ	ε	mμ	ε	mμ	ε
Cl	271	7,300	265	9,100	266	9,000	265	9,300
NH_2	272	9,500	262	12,500	261	13,900		
SCH_3	293	14,000	284	17,800	284	19,100	284	20,600
OH	257	9,150	249	10,200			249	11,100

[a] All spectra were determined in absolute ethanol.

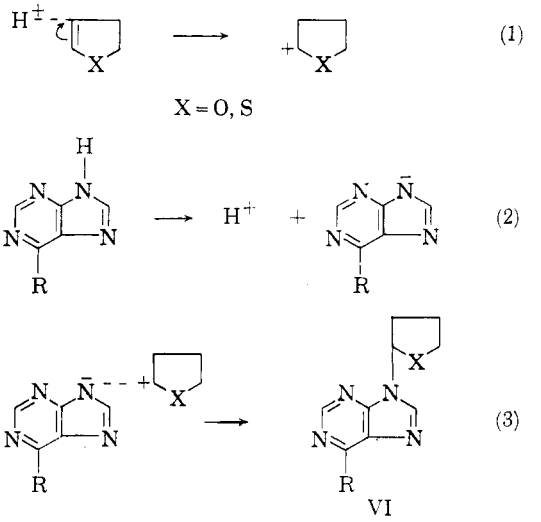
TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF SOME 9-(TETRAHYDRO-2-FURYL)-6-SUBSTITUTED PURINES



	pH 1		pH 11		ethanol	
R	mμ	ε	mμ	ε	mμ	ε
Cl	265	9,400	266	9,600	266	9,000
Br	266	10,800	267	11,300	267	11,600
I	277	9,800	277	11,400	275	11,400
SH	326	17,600	312	20,400	326	17,100
SCH_3	295	14,400	290	17,700	284	19,100
o-$FC_6H_4CH_2S$	294	17,500	293	21,800	285	20,800
	281	16,000	290	18,500	284	20,400
NH_2	263	15,200	261	17,200	261	13,900
$N(CH_3)_2$	277	14,400	276	18,700	275	15,800
$NHCH_2CH_2OH$	273	15,700	268	17,200	268	10,700
$HNCH_3$	267	15,100	267	16,400	266	16,000
CN	289	9,000	289	9,500	288	9,100

general reaction of 2,3-dihydrofuran and 2,3-dihydrothiophene with various 6-substituted purines revealed that the reaction proceeded best if the substituent at position 6 were an electron-withdrawing group. The reaction failed when the substituent at position 6 was hydrogen, amino, hydroxy, mercapto, or dimethylamino. With regard to the 6-halogenated purines, the yield of desired product, IV, decreased with decreasing electronegativity of the halogens. Thus, 6-chloropurine reacted with 2,3-dihydrothiophene to give 65% yield of IV (R = Cl), while 6-bromopurine and 6-iodopurine gave only 30% and 22% of IV (R = Br) and IV (R = I), respectively. These experimental observations are in accord with the following mechanism.



(1) Addition of a proton to the double bond at position 4 of the five-membered ring.

(2) Ionization of the purine to provide an anion at position 9.

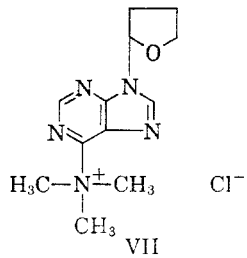
(3) Attraction of the anion (position 9) for the cation of the five-membered ring to form the product, VI.

The reaction proceeded best with a catalytic amount of p-toluenesulfonic acid. When R was a strongly basic group, such as dimethylamino, it is quite possible that the catalytic amount of acid preferentially protonated the purine derivative, and therefore no reaction took place. This interesting type of reaction is presently being extended to include the preparation of several 2,6-disubstituted 9-(tetrahydro-2-furyl)purines. 6-Methylthio-9-(tetrahydro-2-thienyl)-purine, (IV. R = SCH_3), was also prepared by alkylation of 9-(tetrahydro-2-thienyl)-6-purinethiol which was in turn prepared from 6-chloro-9-(tetrahydro-2-thienyl)purine (IV. R = Cl) and methanolic potassium hydrosulfide. Inspection of the spectral data in Table I strongly supports assignment of the tetrahydro-2-thienyl group to position 9. An attempt to react 5-methyl-

(12) B. R. Baker, R. E. Schaub, and J. P. Joseph, *J. Org. Chem.*, **19**, 638 (1954).

(13) S. F. Birsh and D. T. McAllen, *J. Chem. Soc.*, 2556 (1951).

2,3-dihydrofuran with 6-chloropurine was unsuccessful, presumably because of the steric interference of the 5-methyl group. Treatment of 6-chloro-9-(tetrahydro-2-furyl)purine (I) with 1*N* sodium hydroxide in an attempt to prepare the 6-hydroxy derivative resulted in degradation of I to give 6-chloro-4,5-diaminopyrimidine[14] as the only isolatable product. 6-Chloro-9-(tetrahydro-2-thienyl)purine under similar conditions gave approximately 20% yield of the desired 6-hydroxy-9-(tetrahydro-2-thienyl)purine (V), an analog of deoxyinosine. Apparently the tetrahydro-2-thienylpurine derivatives are more stable to treatment with strong base. Reaction of 6-chloro-9-(tetrahydro-2-furyl)purine (I) with trimethylamine in anhydrous benzene gave trimethyl[9-(tetrahydro-2-furyl)-6-purinyl]ammonium chloride (VII), an interesting quaternary salt.



VII

The deoxyadenosine analog, 9-(tetrahydro-2-furyl)adenine (III), 6-chloro-9-(tetrahydro-2-furyl)-purine (I), 9-(tetrahydro-2-furyl)purine (III), and VII have all shown significant antitumor activity against adenocarcinoma 755 in mice. In general the 6-substituted 9-(tetrahydro-2-thienyl)purines are without activity in this test system. These results will be the subject of a separate communication.

EXPERIMENTAL[15]

6-Chloro-9-(tetrahydro-2-furyl)purine (I). To 150 ml. of ethyl acetate were added 10.0 g. of 6-chloropurine[8] and 0.5 g. of *p*-toluenesulfonic acid. The mixture was stirred vigorously at room temperature, and 7.5 g. of 2,3-dihydrofuran[7] was added dropwise over a 30-min. period. The solution was gradually heated to 50°, then allowed to cool to room temperature, and washed once with a saturated solution of aqueous potassium carbonate, then twice with water. The ethyl acetate was dried over anhydrous sodium sulfate and distilled under reduced pressure. The resulting syrup was allowed to crystallize. Recrystallization from petroleum ether (b.p. 60–110°) gave 8.7 g. of product, m.p. 93–95°.

Anal. Calcd. for $C_9H_9N_4ClO$: C, 48.3; H, 4.0; N, 25.0. Found: C, 48.55; H, 3.81; N, 24.7.

6-Bromo-9-(tetrahydro-2-furyl)purine. 6-Bromopurine[16] (7.5 g.) and 0.5 g. of *p*-toluenesulfonic acid were added to 150 ml. of ethyl acetate. The mixture was stirred vigorously at room temperature, and 4.0 g. of 2,3-dihydrofuran was added over a 30-min. period. The solution was then gradually heated to 50° and finally allowed to cool to room temperature. The ethyl acetate was washed once with saturated aqueous potassium carbonate, then twice with water. The solution was then dried over anhydrous sodium sulfate and the excess ethyl acetate distilled under reduced pressure. The resulting syrup crystallized with the addition of 100 ml. of petroleum ether. Recrystallization from petroleum ether (b.p. 60–110°) gave 6.5 g. of product, m.p. 106–108°.

Anal. Calcd. for $C_9H_9N_4BrO$: C, 40.3; H, 3.4; N, 20.8. Found: C, 40.7; H, 3.59; N, 20.6.

6-Iodo-9-(tetrahydro-2-furyl)purine. To 150 ml. of ethyl acetate were added 10.0 g. of 6-iodopurine[16] and 0.5 g. of *p*-toluenesulfonic acid. The reaction mixture was treated and the product isolated as in the preparation of the 6-chloro-9-(tetrahydro-2-furyl)purine (I). Recrystallization from petroleum ether (b.p. 60–110°) gave 12.5 g. of product, m.p. 105–106°.

Anal. Calcd. for $C_9H_9N_4IO$: C, 34.5; H, 2.8; N, 17.7. Found: C, 34.85; H, 2.54; N, 17.5.

9-(Tetrahydro-2-furyl)purine-6-thiol (II). 6-Chloro-9-(tetrahydro-2-furyl)purine (10.0 g.) was dissolved in 125 ml. of absolute methanol. To this solution was added 250 ml. of a solution of sodium hydrosulfide in methanol prepared as follows: A solution of 13.0 g. of sodium in 250 ml. of absolute methanol was saturated with hydrogen sulfide at 10°. The solution was boiled gently on the steam bath for 30 min., filtered, and the filtrate carefully neutralized to *p*H 7 with glacial acetic acid. The solution was then cooled and the solid material filtered. Recrystallization from absolute ethanol gave 6.3 g. of product which decomposed without melting at 248–250°.

Anal. Calcd. for $C_9H_{10}N_4OS$: C, 48.8; H, 4.5; N, 25.2. Found: C, 49.11; H, 4.64; N, 24.9.

6-Methylthio-9-(tetrahydro-2-furyl)purine. To 150 ml. of ethyl acetate were added 5.0 g. of 6-methylthiopurine[11] and 0.5 g. of *p*-toluenesulfonic acid. The mixture was stirred vigorously at room temperature, and 6.5 g. of 2,3-dihydrofuran was added dropwise over a 30-min. period. The reaction mixture was treated as for the preparation of I. The solid was filtered and recrystallized from petroleum ether (b.p. 30–60°) to yield 7.0 g. of product, m.p. 81°.

Anal. Calcd. for $C_{10}H_{12}N_4OS$: C, 50.7; H, 5.1; N, 23.7. Found: C, 50.43; H, 4.76; N, 23.5.

6-o-Fluorobenzylthio-9-(tetrahydro-2-furyl)purine. To 200 ml. of ethyl acetate were added 10.0 g. of 6-*o*-fluorobenzylthiopurine[17] and 1.0 g. of *p*-toluenesulfonic acid. Then with vigorous stirring was added 6.0 g. of 2,3-dihydrofuran, and the mixture was refluxed for 30 min. on the water bath. The resulting solution was then removed from the water bath and, with continued stirring, was allowed to cool to room temperature. The solution was washed once with a saturated aqueous solution of sodium carbonate and twice with water. After drying over a mixture of anhydrous sodium sulfate and sodium carbonate, the excess ethyl acetate was distilled under reduced pressure and the syrupy residue recrystallized from petroleum ether (b.p. 60–110°) to give 9.7 g. of product, m.p. 75–76°.

Anal. Calcd. for $C_{16}H_{15}N_4FOS$: C, 58.2; H, 4.55; N, 17.0. Found: C, 57.8; H, 4.57; N, 16.6.

6-(2-Pyridylmethylthio)purine. To a solution of 10.0 g. of purine-6-thiol[11] in 150 ml. of concd. aqueous ammonium hydroxide was added with vigorous stirring 10.7 g. of 2-chloromethylpyridine hydrochloride.[18] The resulting solution was stirred mechanically, heated at 50° for 1 hr., and then cooled slowly to room temperature. The solution was allowed to stand overnight at room temperature. The solid material was filtered and recrystallized from an ethyl acetate–ethanol mixture to give 15.2 g. of colorless crystals, m.p. 187–188°.

(14) R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Am. Chem. Soc.*, 75, 263 (1953).

(15) All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected unless otherwise indicated.

(16) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, 78, 3508 (1956).

(17) T. P. Johnston, L. B. Holum, and J. A. Montgomery, *J. Am. Chem. Soc.*, 80, 6265 (1958).

(18) Purchased from Aldrich Chemical Co., Inc., 2369 North 29th St., Milwaukee 10, Wis.

Anal. Calcd. for $C_{11}H_9N_5S$: C, 54.3; H, 3.7; N, 28.8. Found: C, 54.27; H, 3.75; N, 28.9.

6-(2-Pyridylmethylthio)-9-(tetrahydro-2-furyl)purine. To 200 ml. of ethyl acetate were added 10.0 g. of 6-(2-pyridylmethylthio)purine and 1.0 g. of *p*-toluenesulfonic acid. 2,3-Dihydrofuran (6.0 g.) was then added with vigorous stirring. With continued stirring the mixture was refluxed on the water bath for 90 min. The solution was then cooled to room temperature and stirred for an additional 30 min. A small amount of insoluble material appeared and was removed by filtration. The filtrate was then washed once with saturated aqueous sodium carbonate, twice with water, and the excess ethyl acetate distilled under reduced pressure. Recrystallization of the syrupy residue from petroleum ether (b.p. 60–110°) gave 4.9 g. of product, m.p. 70–72°.

Anal. Calcd. for $C_{15}H_{15}N_5OS$: C, 57.5; H, 4.9. Found: C, 57.6; H, 5.3.

6-Amino-9-(tetrahydro-2-furyl)purine (III). To 200 ml. of methanol which had previously been saturated with anhydrous ammonia at 0° was added 10.0 g. of 6-chloro-9-(tetrahydro-2-furyl)purine. The resulting solution was allowed to stand at room temperature for 48 hr. in a stoppered flask. The solution was then evaporated to dryness at atmospheric pressure and room temperature. The residue was extracted with three 100-ml. portions of boiling ethyl acetate. The ethyl acetate was then distilled under reduced pressure and the solid residue recrystallized from an ethanol–petroleum ether (b.p. 60–110°) mixture to give 3.2 g. of cream-colored crystals, m.p. 165–168°.

Anal. Calcd. for $C_9H_{11}N_5O$: C, 52.7; H, 5.4; N, 34.1. Found: C, 52.6; H, 5.5; N, 33.7.

6-Dimethylamino-9-(tetrahydro-2-furyl)purine. To 150 ml. of 25% aqueous dimethylamine was added 10.0 g. of 6-chloro-9-(tetrahydro-2-furyl)purine (I), and the solution was heated on the steam bath for 4 hr. The aqueous layer was then decanted, and the oily layer was dissolved in 150 ml. of boiling benzene. The volume was reduced to 50 ml. An equal volume of petroleum ether (b.p. 30–60°) was added, the solution cooled, and the product collected. Recrystallization from *n*-heptane gave 4.8 g. of product, m.p. 83–84°.

Anal. Calcd. for $C_{11}H_{15}N_5O$: C, 56.6; H, 6.4; N, 30.1. Found: C, 56.6; H, 6.4; N, 30.3.

6-(2-Hydroxyethylamino)-9-(tetrahydro-2-furyl)purine. A solution of 5.0 g. of 6-chloro-9-(tetrahydro-2-furyl)purine (I) and 1.35 g. of ethanolamine in 150 ml. of methanol was refluxed for 3 hr. The excess solvent was then distilled under reduced pressure and the residue extracted with three 50-ml. portions of benzene. The benzene solution was concentrated to approximately 50 ml. on the steam bath, the solution cooled overnight in the refrigerator, and the product filtered to give 3.4 g. of white crystals, m.p. 102–103°

Anal. Calcd. for $C_{11}H_{15}N_5O_2$: C, 53.0; H, 6.0; N, 28.1. Found: C, 52.93; H, 6.44; N, 27.8

6-Chloro-9-(tetrahydro-2-thienyl)purine (IV. R = Cl). To 300 ml. of anhydrous ethyl acetate were added 25 g. of 6-chloropurine,[8] 0.25 g. of *p*-toluenesulfonic acid, and 45 ml. of 2,3-dihydrothiophene.[13] The mixture was refluxed and stirred for 10 hr. then filtered from 2 g. of unchanged 6-chloropurine. The filtrate was treated with charcoal, then washed with 150 ml. of saturated sodium carbonate solution and finally with 150 ml. of water. The ethyl acetate solution was dried over anhydrous sodium sulfate and then evaporated under reduced pressure at 70°. The syrupy residue crystallized upon standing. The solid was suspended in petroleum ether (b.p. 20–40°) and filtered to yield 28.5 g. of crude product. Recrystallization from a petroleum ether (b.p. 60–110°) and ethyl acetate mixture gave an 80% recovery of product, m.p. 110–111°.

Anal. Calcd. for $C_9H_9N_4SCl$: C, 45.1; H, 3.75; N, 23.4. Found: C, 45.2; H, 3.86; N, 23.4.

9-(tetrahydro-2-thienyl)purine-6-thiol. Ten grams of 6-chloro-9-(tetrahydro-2-thienyl)purine (IV. R = Cl) was dissolved in 125 ml. of absolute methanol. To this solution was added 250 ml. of a solution of sodium hydrosulfide (1*N*) in methanol. The solution was boiled on a steam bath for 30 min., filtered, and the filtrate neutralized to *p*H 7 with glacial acetic acid while in an ice bath. After cooling for 30 min. the white solid was filtered to yield 9.4 g. of product which decomposed at 255°. A small amount was recrystallized from *N,N*-dimethylacetamide.

Anal. Calcd. for $C_9H_{10}N_4S_2$: C, 45.4; H, 4.20; N, 23.5. Found: C, 45.6; H, 4.60; N, 23.6.

6-Bromo-9-(tetrahydro-2-thienyl)purine (IV. R = Br). The procedure employed was identical to that for the preparation of 6-chloro-9-(tetrahydro-2-thienyl)purine except that 6-bromopurine[16] was used instead of 6-chloropurine. The yield was 30.4% of a product recrystallized from petroleum ether to give a m.p. of 120–121°. Ultraviolet absorption in ethanol: λ_{max} 267 mμ, ϵ_{max} 11,200.

Anal. Calcd. for $C_9H_9N_4SBr$: C, 37.9; H, 3.16; N, 19.6. Found: C, 38.17; H, 3.28; N, 19.5.

6-Iodo-9-(tetrahydro-2-thienyl)purine (IV. R = I). The procedure employed was identical to that for the preparation of 6-chloro-9-(tetrahydro-2-thienyl)purine except that 6-iodopurine[16] was used instead of 6-chloropurine. The yield of 6-iodo-9-(tetrahydro-2-thienyl)purine was 12.5%, m.p. 123–124°. Ultraviolet absorption in ethanol: λ_{max} 277 mμ, ϵ_{max} 12,000.

Anal. Calcd. for $C_9H_9N_4SI$; C, 32.5; H, 2.71; N, 16.9. Found: C, 33.0; H, 2.7; N, 16.5.

6-Hydroxy-9-(tetrahydro-2-thienyl)purine (V). 6-Chloro-9-(tetrahydro-2-thienyl)purine (IV. R = Cl) (1.0 g.) was stirred in 15 ml. of 1*N* sodium hydroxide for 30 min. and filtered from a small amount of oily residue. The hot filtrate was carefully adjusted to *p*H 7 with glacial acetic acid and allowed to stand at 10° for 30 min. The white solid which appeared was filtered to give 0.25 g. of product, m.p. 190–195°. Recrystallization from an ethyl acetate and methanol mixture raised the melting point to 203–205°.

Anal. Calcd. for $C_9H_{10}N_4SO$: C, 48.7; H, 4.50; N, 25.2. Found: C, 48.4; H, 4.4; N, 24.9.

6-Methylthio-9-(tetrahydro-2-thienyl)purine (IV. R = SCH_3). *Method 1.* To 50 ml. of ammonium hydroxide was added 1 g. of 9-(tetrahydro-2-thienyl)purine-6-thiol. The mixture was stirred at 35° until solution resulted. One gram of methyl iodide was then added and stirring continued at 35° for 30 min. The solid that formed was filtered to yield 0.9 g. of product, m.p. 118–121°. Recrystallization from a mixture of petroleum ether (b.p. 60–110°) and ethyl acetate raised the melting point to 126–128°.

Method 2. To 300 ml. of ethyl acetate were added 20 g. of 6-methylthiopurine,[11] 0.25 g. of *p*-toluenesulfonic acid, and 13 g. of 2,3-dihydrothiophene. The mixture was stirred and refluxed for 10 hr., cooled, and finally filtered to remove 12.5 g. of starting material (6-methylthiopurine). The filtrate was washed once with 100 ml. of saturated sodium carbonate solution and once with 100 ml. of water. The excess solvent was removed under vacuum to give an oily residue which solidified upon standing. Recrystallization from a mixture of petroleum ether (b.p. 60–110°) and ethyl acetate gave 3.8 g. of product, m.p. 117–120°. Another recrystallization raised the melting point to 125–127°. A mixed melting point with that product prepared by method 1 showed no depression.

Anal. Calcd. for $C_{10}H_{12}N_4S_2$: C, 47.7; H, 4.77; N, 22.2. Found: C, 47.44; H, 4.93; N, 22.0.

Basic degradation of 6-chloro-9-(tetrahydro-2-furyl)purine (I). To 10 ml. of 1*N* sodium hydroxide was added 0.5 g. of 6-chloro-9-(tetrahydro-2-furyl)purine (I). The solution was stirred at 80° for 30 min. The cooled solution deposited 0.2 g. of tan crystals, m.p. 249–251° dec. Recrystallization from water raised the melting point to 253–254° dec. A mixed melting point with an authentic sample of 6-chloro-4,5-diaminopyrimidine[14] gave a m.p. of 252–254° dec. The product also exhibited ultraviolet absorption spectra at *p*H

11 and *p*H 1 identical to that of 6-chloro-4,5-diaminopyrimidine.

Anal. Calcd. for $C_4H_5N_4Cl$: C, 33.3; H, 3.46. Found: C, 33.7; H, 3.88.

6-Methylamino-9-(tetrahydro-2-furyl)purine. 6-Chloro-9-(tetrahydro-2-furyl)purine (I) (1.5 g.) was added to 75 ml. of 40% aqueous methylamine and the solution heated on a steam bath for 1 hr. The solution was then reduced to an oil under vacuum and the syrupy residue recrystallized from a mixture of petroleum ether (b.p. 60–110°) and ethyl acetate to yield 0.9 g. of white crystals, m.p. 103–104°.

Anal. Calcd. for $C_{10}H_{13}N_5O$: C, 54.8; H, 5.94. Found: C, 54.6; H, 5.79.

6-Cyano-9-(tetrahydro-2-furyl)purine. 6-Cyanopurine[10] (2.0 g.) was stirred in 75 ml. of ethyl acetate with *p*-toluenesulfonic acid (0.1 g.) present, while 1.0 g. of 2,3-dihydrofuran was added over a period of 30 min. at room temperature. After stirring for 2 hr. at 50° the solution was treated with charcoal and filtered. The filtrate was washed once with 50 ml. of saturated sodium carbonate and once with 75 ml. of water, then dried over anhydrous sodium sulfate. Upon removal of the ethyl acetate under reduced pressure, an oily residue remained which solidified upon standing. Recrystallization from a mixture of petroleum ether (b.p. 60–110°) and ethyl acetate yielded 1.3 g. of crystalline product. A second recrystallization from the same solvent mixture gave a product of m.p. 92–93°.

Anal. Calcd. for $C_{10}H_9N_5O$: C, 55.8; H, 4.18; N, 32.6. Found: C, 55.8; H, 4.50; N, 32.4.

Trimethyl[9-(tetrahydro-2-furyl)-6-purinyl]ammonium chloride. To a solution of 3 g. of anhydrous trimethylamine, dissolved in 30 ml. of anhydrous benzene, was carefully added a solution of 5.0 g. of 6-chloro-9-(tetrahydro-2-furyl)purine, dissolved in 50 ml. of anhydrous benzene. The solution was allowed to stand at room temperature for 30 min. Reaction took place almost immediately as evidenced by the formation of a white precipitate. This precipitate was removed by filtration and recrystallized from an absolute ethanol-ether mixture to yield 6.2 g., m.p. 148°.

Anal. Calcd. for $C_{12}H_{18}N_5OCl$: C, 50.8; H, 6.36. Found: C, 50.5; H, 6.54.

Acknowledgment. The authors are indebted to James J. Sims who prepared trimethyl[9-(tetrahydro-2-furyl)-6-purinyl]ammonium chloride (VII) for this study.

TEMPE, ARIZ.

[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH DEPARTMENT, SCHERING CORP.]

3-Substituted Dihydrobenzothiadiazine 1,1-Dioxides as Diuretic Agents[1]

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Received April 6, 1961

A series of 3-substituted 3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides has been synthesized by the condensation of substituted orthanilamides with aldehydes and the compounds tested for their efficacy as diuretic agents. Some side products and unusual reactions which occurred in the application of the general synthetic method have been examined.

The discovery of chlorothiazide, 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (I. Y = R = H, X = Cl), as an orally effective diuretic agent with a concomitant favorable effect on electrolyte excretion rates announced in 1957 by Novello and Sprague[2] has led to a major advance in diuretic therapy. We have been engaged in preparing other compounds of the 1,2,4-benzothiadiazine type with the object of finding new agents with superior diuretic properties. Saturation of the 3,4- double bond in I (Y = R = H, X = Cl) resulted in a compound with at least ten times the potency of chlorothiazide.[3] Our research has resulted in the synthesis of a series of 3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides (II) with emphasis placed on substituents at position 3. Recently other reports of work in this area have appeared.[4]

From our studies, 6-chloro-3-dichloromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-di-

(1) Presented in part before the Division of Medicinal Chemistry, 136th Meeting of the American Chemical Society, Atlantic City, N. J., September 1959.

(2) F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.*, **79**, 2028 (1957).

(3) While this work was in progress, G. de Stevens, L. H. Werner, A. Halamandaris, and S. Ricca, Jr., *Experientia*, **14**, 463 (1958) described the synthesis and diuretic activity of hydrochlorothiazide, 6-chloro-3,4-dihydro-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (II. Y = R = H; X = Cl).

(4)(a) M. E. Goldberg and K. Hwang, Federation Meeting, Atlantic City, N. J., September 1959. (b) J. M. McManus, A. Scriabine, S. Y. Pan, W. M. McLamore, and G. D. Laubach, American Chemical Society Meeting, Atlantic City, N. J., September 1959. (c) R. M. Taylor and M. M. Winbury, *Pharmacologist*, **1**, 53, Fall 1959, No. 2; (d) C. T. Holdrege, R. B. Babel, and Lee C. Cheney, *J. Am. Chem. Soc.*, **81**, 4807 (1959). (e) W. J. Close, L. R. Swett, L. E. Brady, J. H. Short, and M. Vesusten, *J. Am. Chem. Soc.*, **82**, 1132 (1960). (f) J. H. Short and U. Biermacher, *J. Am. Chem. Soc.*, **82**, 1135 (1960). (g) L. H. Werner, A. Halamandaris, S. Ricca, Jr., L. Dorfman, and G. de Stevens, *J. Am. Chem. Soc.*, **82**, 1161 (1960). (h) H. L. Yale, K. Losee and J. Bernstein, *J. Am. Chem. Soc.*, **82**, 2042 (1960). (i) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 965 (1960). (j) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler and J. M. Sprague, *J. Org. Chem.*, **25**, 970 (1960). (k) C. Pelayo, J. Iriarte, and H. J. Ringold, *J. Org. Chem.*, **25**, 1067 (1960). (l) F. J. Lund and W. Kobinger, *Acta Pharmacol. Toxicol.*, **16**, 297 (1960).