acetimide (0.108 g.) was added as a slurry in 100 ml. of dry ether in small portions to the suspension of the N^{α}-tosyl-DL-lysine benzyl ester (0.178 g.) in 300 ml. of dry ether during the course of 15 min. After the mixture had been stirred an additional 10 min., the clear, pale pink solution was cooled in an ice bath. Dry hydrogen chloride was passed into the solution, which resulted in the immediate appearance of a white, flocculent precipitate. After standing for 10 min., the product was collected by centrifugation and washed five times with 30 ml. of ether. After drying *in vacuo* over potassium hydroxide, there was obtained 0.251 g. of III hydrochloride (83%), which melted indefinitely above 100–105°, turning red and becoming viscous during heating. Attempts to crystallize the hydrochloride were not successful.

Anal. Calcd. for $C_{35}H_{38}N_3O_6ClS$: C, 63.3; H, 5.77. Found: C, 62.6; H, 5.83.

N^{ϵ}-(1-Hydroxy-2-acetamido-4-fluorenyl)-DL-lysine (IV). A mixture of 0.238 g. of III (0.38 mmole) and 0.110 g. of phenol (1.16 mmoles) was suspended in 2 ml. of 37% hydrogen bromide in glacial acetic acid in a glass-stoppered 10 ml. Erlenmeyer flask and heated at 70° for 2 hr.[8] The clear brown solution was then cooled to room temperature and 6 ml. of ether was added. The precipitate was collected by centrifugation and washed five times with 10 ml. of ether. The tan colored product, which was very hygroscopic, was dissolved in 5 ml. of 50% ethanol and the red-brown solution was passed through a column (1 × 10 cm.) of IRA-400 (acetate). The column was washed with 50% ethanol and the fractions containing ninhydrin-positive material were collected, combined and concentrated under reduced pressure at 35° to approximately one-half volume. The mixture was centrifuged to remove a small amount of precipitate and the slightly turbid supernatant solution was lyophilized. There was obtained 0.104 g. of crude IV (68% yield). The compound became red at about 155° and turned brown, becoming viscous, at 165–168°. The crude IV was purified by dissolving 58.6 mg. in 2.5 ml. of warm methanol. A small amount of insoluble material (4.7 mg.), which was gray-black and did not melt below 300°, was removed by centrifugation. The clear red supernatant solution was filtered through charcoal and the charcoal was washed with methanol. The filtrate and washings were combined, diluted with ether to incipient turbidity and cooled. The brown-red product was collected by centrifugation and washed with ether. After drying *in vacuo*, there was obtained 10.5 mg. of IV. The product softened at 160–162° and melted at 171–174°.

Anal. Calcd. for $C_{21}H_{25}N_3O_4 \cdot H_2O$: C, 62.8; H, 6.78; N, 10.47. Found: C, 63.0; H, 6.40; N, 10.44.

The ultraviolet spectrum of IV in 95% ethanol showed λ_{max} = 292 mμ (ε, 15,000) and λ_{min} = 253 mμ (ε, 7760).

IV was soluble in Methyl Cellosolve, ethanol, methanol, and very soluble in 50% aqueous ethanol or methanol, but insoluble in chloroform, ether, water, dioxane, toluene, or acetone. The compound gave a strongly positive ninhydrin reaction as well as a positive reaction with the Folin-Ciocalteau reagent.

On paper chromatograms, IV (10–30 μg.) was detected by spraying separate strips with ninhydrin solution (0.3% in ethanol) or with the Folin-Ciocalteau reagent as described above. The most suitable solvent was 1-butanol:acetic acid: water (4:1:5). Using this solvent and the descending technique with 15–18 hr. development time, a single spot (R_f = 0.53), giving *both* a positive ninhydrin reaction and a positive Folin reaction, was obtained. In addition, there was a spot which gave only a positive ninhydrin reaction (R_f, 0.20); this spot was shown to be due to lysine. All samples of IV were contaminated with traces of lysine. Using the solvent systems listed below and the ascending technique with shorter development times, a single spot was obtained for IV except that there were traces of lysine as indicated: *tert*-butyl alcohol:formic acid:water 70:15:15 (R_f of IV, 0.55), methyl ethyl ketone:propionic acid:water 75:25:30 (R_f of IV, 0.51, R_f of lysine, 0.10) and phenol:water 88:12 (R_f of IV, 0.98). The compound did not migrate in the solvent system cyclohexane: *tert*-butyl alcohol:pyridine:water (16:2:2:1).

In subsequent experiments, it was found to be more expeditious to detect IV by the use of paper electrophoresis. Using the Beckman Spinco Model R paper electrophoresis cell and Duostat power supply and Whatman 3MM paper with 0.25*N* acetic acid as the electrolyte, IV was readily separated from the contaminating lysine with a constant voltage of 200 volts (about 2.2 milliamps) in 2.5 hr. The mobilities (cm./sec. per volt/cm.) of IV and lysine were 6.7 and 15, respectively, under these conditions. The compounds were detected after electrophoresis on the air-dried strips as described above for the paper chromatography of IV.

MINNEAPOLIS, MINN.

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Derivatives of 7-Methyl-6-thia-1,6-dihydro- and 7-Methyl-6-thia-1,2,3,6-tetrahydropurine 6,6-Dioxide

F. F. BLICKE AND CHEUK-MAN LEE[1,2]

Received July 13, 1960

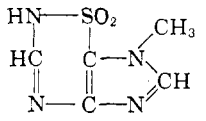
Derivatives of 7-methyl-6-thia-1,6-dihydro- (A) and 7-methyl-6-thia-1,2,3,6-tetrahydropurine 6,6-dioxide (B), as well as the parent compound A, have been prepared by interaction of 1-methyl-4-amino-5-sulfamylimidazole with ortho esters, phosgene or thiophosgene.

A number of derivatives of 1-methyl-4-nitro- and 1-methyl-4-amino-5-substituted imidazoles were synthesized.

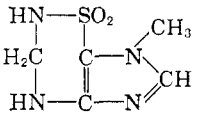
This paper describes the preparation of derivatives of 7-methyl-6-thia-1,6-dihydro- (A) and 7-methyl-6-thia-1,2,3,6-tetrahydropurine-6,6-dioxide (B). These products were of interest as potential antimetabolites. In addition, the parent compound A has been synthesized.

(1) This paper represents part of a dissertation submitted by Cheuk-Man Lee for the Ph.D. degree in the University of Michigan.

(2) This work was supported by a grant (CY-3581) from the U. S. Department of Health, Education and Welfare, U. S. Public Health Service.



A



B

As the purine ring system was obtained by the use of imidazole derivatives, we prepared, initially, a number of 1-methyl-4-nitro-5-substituted-imidazoles (Table I, compounds 1–23) in the manner shown in Reaction Scheme A from 1-methyl-4-nitro-5-chloroimidazole (I). The required imidazole (I) was obtained, in three steps, from diethyl oxalate by known procedures. The disulfide (23) was prepared by oxidation of II with hydrogen peroxide.

The nitro compound II was reduced to the corresponding amino compound (24) by the use of sodium hydrosulfite, and the nitro derivatives 9–12 and 14–17 were reduced with hydrogen and Raney nickel (Table II). When the nitro compound 1-methyl-4-nitro-5-(dimethylaminomethylenesulfamyl)imidazole (13) was reduced, it was converted into 1-methyl-4-amino-5-(dimethylaminomethylsulfamyl)imidazole (38). Crystalline products could not be obtained after hydrogenation of the other nitro compounds listed in Table I.

When 1-methyl-4-amino-5-sulfamylimidazole (25) and the 4-amino compounds 33, 43, and 46 were heated with formic acid on a steam bath, the corresponding 4-formylamino derivatives, 27, 35, 44, and 47, respectively, were formed.

Interaction of the 4-amino compounds 25, 39, and 48, with acetic anhydride in ethanol yielded the corresponding 4-acetylamino derivatives 28, 41, and 50, respectively.

By employing acetic anhydride and pyridine, compounds 39, 43, and 48 were converted into the corresponding 4-diacetylamino derivatives 42, 45, and 51, respectively, while 25 was converted into 4-(diacetylamino)-5-(acetylsulfamyl)imidazole (32).

Reaction between 25 and butyric anhydride yielded the 4-butyrylamino derivative (29). Treatment of 25 with ethyl chloroformate and pyridine yielded 1-methyl-4-(carbethoxyamino)-5-sulfamylimidazole (31). By the use of the hydrochloride of 25 and potassium cyanate, the 4-carbamylamino compound (30) was obtained.

Unsuccessful attempts were made to condense VII with urea, ethyl chloroformate or diethyl carbonate to form IXa, with formamide to produce VIIIa, and with acetic anhydride to yield VIIIb.

Products of types VIII (or VIII′) or IXa could not be obtained by the action of heat, dilute sulfuric acid or aqueous sodium hydroxide on compounds 27–31 and 35 (Table II).

Treatment of VII with formic acid, ethyl orthoformate, ethyl orthoacetate, and ethyl orthopropionate, respectively, yielded products of type VIII (or VIII′) shown in Reaction Scheme B.

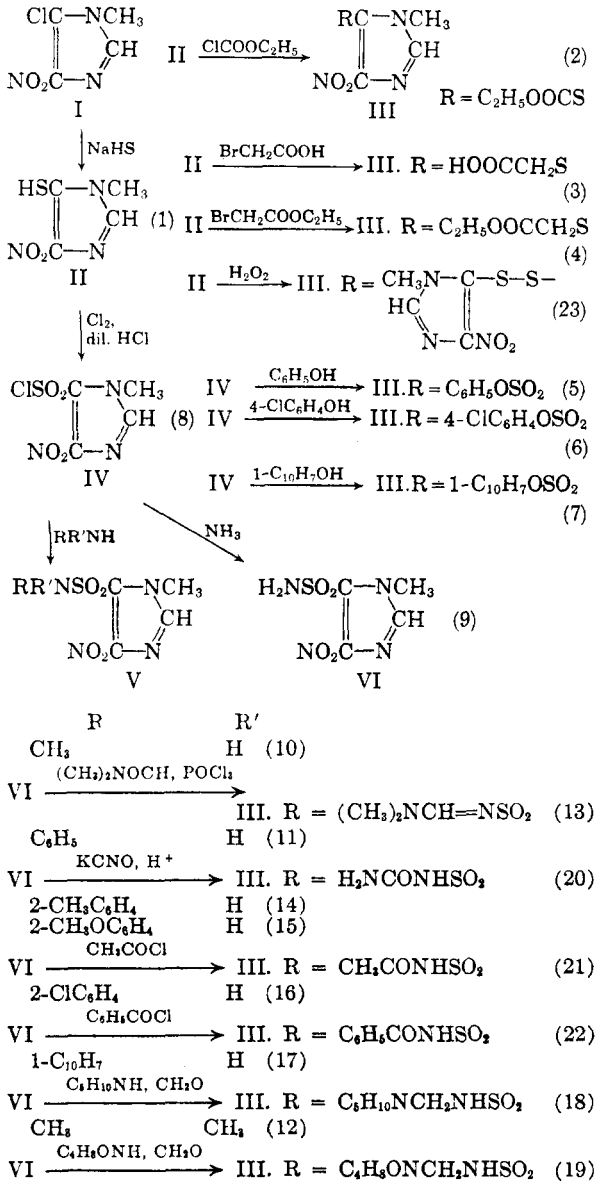
Although it has been found[3] that *o*-amino-*N*-substituted sulfamylbenzenes could be condensed with ethyl orthoformate to form 1,2,4-benzothiadiazine dioxides, we were unable to prepare compounds of type VIII by condensation of ethyl orthoformate with compounds 33, 39, 43, 46, and 48.

Compound VII was converted by phosgene and thiophosgene, respectively, into products of type IX.

When IXa was allowed to react with dimethyl sulfate, a mixture of the alkali-insoluble product X and the alkali-soluble product XI was obtained.

Compound XII, when treated with phosgene and thiophosgene, respectively, yielded products of type XIII.

Reaction Scheme A

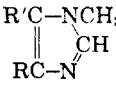


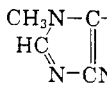
R	R′		
CH3	H	(10)	
VI $\xrightarrow{(CH_3)_2NOCH,\ POCl_3}$ III. R = $(CH_3)_2NCH{=}NSO_2$		(13)	
C_6H_5	H	(11)	
VI $\xrightarrow{KCNO,\ H^+}$ III. R = $H_2NCONHSO_2$		(20)	
2-$CH_3C_6H_4$	H	(14)	
2-$CH_3OC_6H_4$	H	(15)	
VI $\xrightarrow{CH_3COCl}$ III. R = $CH_3CONHSO_2$		(21)	
2-ClC_6H_4	H	(16)	
VI $\xrightarrow{C_6H_5COCl}$ III. R = $C_6H_5CONHSO_2$		(22)	
1-$C_{10}H_7$	H	(17)	
VI $\xrightarrow{C_5H_{10}NH,\ CH_2O}$ III. R = $C_5H_{10}NCH_2NHSO_2$		(18)	
CH_3	CH_3	(12)	
VI $\xrightarrow{C_4H_8ONH,\ CH_2O}$ III. R = $C_4H_8ONCH_2NHSO_2$		(19)	

(3) J. H. Freeman and E. C. Wagner, *J. Org. Chem.*, **16**, 815 (1951).

TABLE I

5-SUBSTITUTED 1-METHYL-4-NITROIMIDAZOLES (COMPOUNDS 1-23)



	R	R′	M.P.	Yield, %		Carbon		Hydrogen		Nitrogen	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
1	NO_2	HS	193–196, dec.	100[a]	$C_4H_5O_2N_3S$	30.18	30.00	3.14	2.94	26.38	25.94
2	NO_2	C_2H_5OOCS	71–72	78	$C_7H_9O_4N_3S$	36.37	36.37	3.92	3.99	18.19	18.04
3	NO_2	$HOOCCH_2S$	202–203	64	$C_6H_7O_4N_3S$	33.18	33.07	3.25	3.01	19.34	19.10
4	NO_2	$C_2H_5OOCCH_2S$	62–63	51	$C_8H_{11}O_4N_3S$	39.19	39.05	4.52	4.54	17.13	17.25
5	NO_2	$C_6H_5OSO_2$	63–64	79	$C_{10}H_9O_5N_3S$	42.40	42.40	3.20	3.22	14.83	14.87
6	NO_2	$4\text{-}ClC_6H_4OSO_2$	117–118	25	$C_{10}H_8O_5N_3SCl$	37.79	37.82	2.54	2.51	13.22	13.22
7	NO_2	$1\text{-}C_{10}H_7OSO_2$	134–135	36	$C_{14}H_{11}O_5N_3S$	50.45	50.65	3.33	3.35	12.61	12.58
8	NO_2	$ClSO_2$	105–106	79	$C_4H_4O_4N_3SCl$	21.29	21.21	1.78	1.77	18.62	18.30
9	NO_2	H_2NSO_2	172–173	79	$C_4H_6O_4N_4S$	23.30	23.30	2.93	3.04	27.17	26.95
10	NO_2	CH_3NHSO_2	136–138	59	$C_5H_8O_4N_4S$	27.27	27.29	3.66	3.71	25.44	25.25
11	NO_2	$C_6H_5NHSO_2$	134–135	80	$C_{10}H_{10}O_4N_4S$	42.54	42.67	3.57	3.66	19.85	19.91
12	NO_2	$(CH_3)_2NSO_2$	101–102	50	$C_6H_{10}O_4N_4S$	30.76	30.78	4.30	4.35	23.92	23.86
13	NO_2	$(CH_3)_2NCH{=}NSO_2$	150–151	54	$C_7H_{11}O_4N_5S$	32.19	32.38	4.24	4.21	26.81	26.47
14	NO_2	$2\text{-}CH_3C_6H_4NHSO_2$	180–181	68	$C_{11}H_{12}O_4N_4S$	44.58	44.45	4.07	4.11	18.91	18.74
15	NO_2	$2\text{-}CH_3OC_6H_4NHSO_2$	128–129	79	$C_{11}H_{12}O_5N_4S$	42.30	42.41	3.87	3.88	17.94	17.65
16	NO_2	$2\text{-}ClC_6H_4NHSO_2$	150–151	84	$C_{10}H_9O_4N_4SCl$	37.92	37.83	2.86	2.87	17.69	17.71
17	NO_2	$1\text{-}C_{10}H_7NHSO_2$	170–171	51	$C_{14}H_{12}O_4N_4S$	50.59	50.65	3.64	3.60	16.86	16.68
18	NO_2	$C_5H_{10}NCH_2NHSO_2$	65–67	100[a]	$C_{10}H_{17}O_4N_5S$	39.59	38.28	5.65	5.44	23.09	22.31
19	NO_2	$C_4H_8ONCH_2NHSO_2$	143–144	82	$C_9H_{15}O_5N_5S$	35.40	35.39	4.95	4.98	22.94	22.66
20	NO_2	$H_2NCONHSO_2$	184–185	47	$C_5H_7O_5N_5S$	24.10	24.12	2.83	2.86	28.10	27.61
21	NO_2	$CH_3CONHSO_2$	211–212, dec.	68	$C_6H_8O_5N_4S$	29.03	29.13	3.24	3.20	22.56	22.30
22	NO_2	$C_6H_5CONHSO_2$	183–184, dec.	40	$C_{11}H_{10}O_5N_4S$	42.57	42.53	3.24	3.18	18.06	17.76
23	NO_2		203–205, dec.	50	$C_8H_8O_4N_6S_2$	30.38	30.13	2.53	2.51	26.59	25.89

[a] Crude yield: Compounds 5, 6, 11, 14–16, 19, 21 and 23 were recrystallized from ethanol; 12 from aqueous ethanol; 1 and 7 from methanol; 3, 9, 10, 20 and 22 from water; 17 from acetic acid; 2 and 4 from aqueous acetic acid; 8 from chloroform; 13 from acetone.

EXPERIMENTAL

1-Methyl-4-nitro-5-mercaptoimidazole[4] (1). A slow stream of hydrogen sulfide was passed into an ice cold solution of sodium ethylate, prepared from 55.0 g. of sodium and 1000 ml. of absolute ethanol, for 4 hr. After the addition of 183.0 g. of 1-methyl-4-nitro-5-chloroimidazole,[5] the mixture was stirred and heated at 50–55° for 12 hr. and then refluxed for 4 hr. It was cooled, 800 ml. of water was added to dissolve the solid, and concentrated hydrochloric acid was added, dropwise, until the mixture was acidic (Congo Red). The precipitate was filtered, washed with water, and dried.

1-Methyl-4-nitro-5-(carbethoxythio)imidazole (2). Ethyl chloroformate (21.7 g., 0.2 mole) was added, gradually, to a stirred solution of 31.8 g. (0.2 mole) of 1-methyl-4-nitro-5-mercaptoimidazole in 80 ml. of 10% alcoholic sodium hydroxide. The mixture was refluxed for 3 hr., cooled, diluted with 800 ml. of water, and extracted with ether. The extract was washed with water, dried, and the solvent was evaporated. The residue solidified when cooled.

1-Methyl-4-nitro-5-(carboxymethylthio)imidazole (3). Bromoacetic acid (13.9 g., 0.1 mole) was added, gradually, to a stirred solution of 15.9 g. (0.1 mole) of 1-methyl-4-nitro-5-mercaptoimidazole in 100 ml. of 4% aqueous sodium hydroxide. After several hours, the mixture was acidified (Congo Red) with concentrated hydrochloric acid wherefrom the product precipitated.

1-Methyl-4-nitro-5-(carbethoxymethylthio)imidazole (4). Ethyl bromoacetate (16.7 g., 0.1 mole) was added, gradually, to a stirred solution of 15.9 g. (0.1 mole) of 1-methyl-4-nitro-5-mercaptoimidazole in 100 ml. of 4% aqueous sodium hydroxide. After several hours, the precipitated product was filtered.

1-Methyl-4-nitro-5-(phenoxysulfonyl)imidazole (5) (and Compounds 6 and 7). 1-Methyl-4-nitro-5-(chlorosulfonyl)-imidazole (8) (22.5 g., 0.1 mole) was added to a solution of 9.4 g. (0.1 mole) of phenol in 31.6 g. (0.4 mole) of pyridine which was cooled in an ice salt bath. After 3 hr., the mixture was treated with 200 ml. of 2*N* hydrochloric acid and the product was filtered.

Compounds 6 and 7 were prepared in the same manner from 8 and the required phenol.

1-Methyl-4-nitro-5-(chlorosulfonyl)imidazole (8). A suspension of 79.5 g. of 1-methyl-4-nitro-5-mercaptoimidazole (1) in 900 ml. of 2*N* hydrochloric acid was stirred and cooled in an ice salt bath. Chlorine was introduced for 4 hr. The suspended material was filtered, washed with ice cold water, filtered, air-dried, and recrystallized from chloroform.

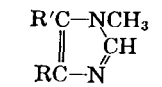
1-Methyl-4-nitro-5-sulfamylimidazole (9) (and Compound 10). A stream of ammonia gas was passed into a stirred solution of 90 g. of 1-methyl-4-nitro-5-(chlorosulfonyl)imidazole (8) in 350 ml. of *p*-dioxane for about 1 hr. The precipitate was filtered, and washed with cold water.

(4) This compound, prepared by a different method, was isolated only as the ammonium salt by L. L. Bennett and H. T. Baker [*J. Am. Chem. Soc.*, **79**, 2188 (1957)].

(5) F. F. Blicke and H. C. Godt, Jr., *J. Am. Chem. Soc.*, **76**, 3653 (1954).

TABLE II

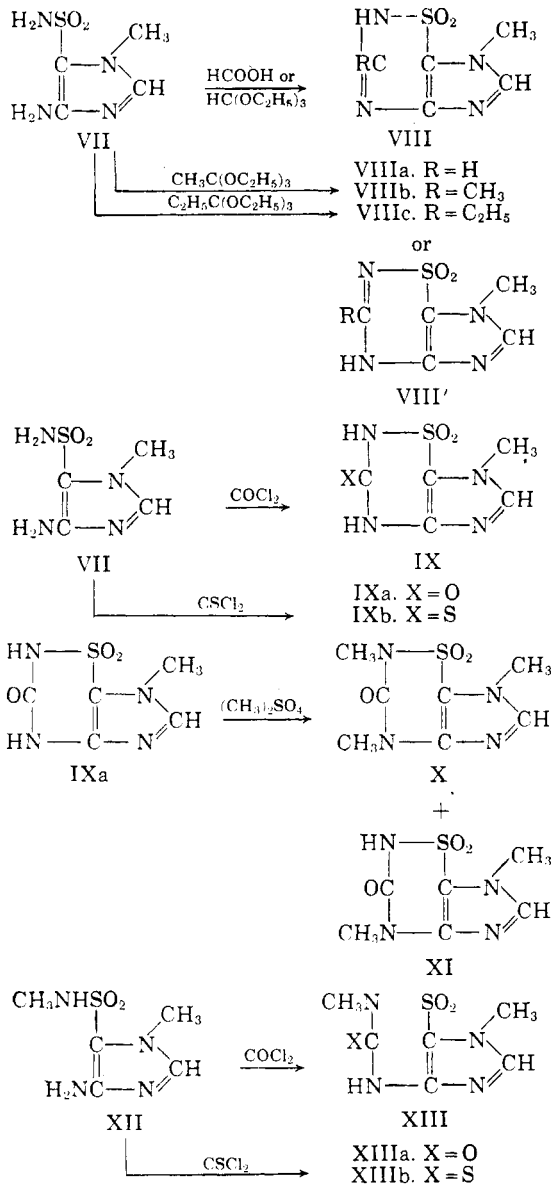
4,5-Disubstituted 1-Methylimidazoles (Compounds 24–52[a])



	R	R′	M.P.	Yield, %	Formula	Carbon		Hydrogen		Nitrogen	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
24	$H_2N.HCl$	HS	174–175, dec.	11	$C_4H_8N_3SCl$	29.01	29.04	4.87	4.78	25.37	25.54
25	H_2N	H_2NSO_2	168–169, dec.	58	$C_4H_8O_2N_4S$	27.26	27.41	4.57	4.50	31.80	31.41
26	$H_2N.HCl$	H_2NSO_2	164–165, dec.	50	$C_4H_9O_2N_4SCl$	22.59	22.81	4.27	4.46	26.34	26.46
27	HCONH	H_2NSO_2	189–190, dec.	24	$C_5H_8O_3N_4S$	29.42	29.51	3.94	3.94	27.44	27.50
28	CH_3CONH	H_2NSO_2	184–185	37	$C_6H_{10}O_3N_4S$	33.02	33.06	4.62	4.67	25.67	25.70
29	$CH_3CH_2CH_2CONH$	H_2NSO_2	170–171	33	$C_8H_{14}O_3N_4S$	39.02	38.99	5.73	5.79	22.75	22.67
30	H_2NCONH	H_2NSO_2	169–171	48	$C_5H_9O_3N_5S$	27.40	27.32	4.14	4.15	31.95	32.16
31	C_2H_5OOCNH	H_2NSO_2	165–166	35	$C_7H_{12}O_4N_4S$	33.86	33.81	4.87	4.91	22.56	22.85
32	$(CH_3CO)_2N$	$CH_3CONHSO_2$	209–211	53	$C_{10}H_{14}O_5N_4S$	39.73	39.69	4.66	4.61	18.54	19.29
33	H_2N	CH_3NHSO_2	137–138, dec.	31	$C_5H_{10}O_2N_4S$	31.58	31.66	5.30	5.38	29.46	29.47
34	$H_2N.HCl$	CH_3NHSO_2	151–152, dec.	57	$C_5H_{11}O_2N_4SCl$	26.49	26.73	4.89	4.98	24.71	24.81
35	HCONH	CH_3NHSO_2	144–145	53	$C_6H_{10}O_3N_4S$	33.02	33.07	4.63	4.65	25.67	25.31
36	H_2N	$(CH_3)_2NSO_2$	128–129	46	$C_6H_{12}O_2N_4S$	35.39	35.31	5.92	5.83	27.43	27.74
37	$H_2N.HCl$	$(CH_3)_2NSO_2$	151–152, dec.	40	$C_6H_{13}O_2N_4SCl$	29.94	29.84	5.44	5.33	23.28	23.62
38	H_2N	$(CH_3)_2NCH_2NHSO_2$	141–142	60	$C_7H_{11}O_4N_5S$	36.03	36.15	6.48	6.31	30.01	30.23
39	H_2N	$C_6H_5NHSO_2$	148–149	48	$C_{10}H_{12}O_2N_4S$	47.60	47.60	4.79	4.71	22.20	22.12
40	$H_2N.HCl$	$C_6H_5NHSO_2$	165–166, dec.	72	$C_{10}H_{13}O_2N_4SCl$	41.59	41.43	4.54	4.64	19.41	19.76
41	CH_3CONH	$C_6H_5NHSO_2$	153–154	41	$C_{12}H_{14}O_3N_4S$	48.98	48.78	4.79	4.77	19.04	18.80
42	$(CH_3CO)_2N$	$C_6H_5NHSO_2$	176–178	55	$C_{14}H_{16}O_4N_4S$	49.99	49.87	4.80	4.98	16.66	17.08
43	H_2N	$2\text{-}CH_3C_6H_4NHSO_2$	156–157, dec.	79	$C_{11}H_{14}O_2N_4S$	49.60	49.62	5.29	5.29	21.04	21.22
44	HCONH	$2\text{-}CH_3C_6H_4NHSO_2$	151–153	22	$C_{12}H_{14}O_3N_4S$	48.97	48.91	4.79	4.61	19.04	19.22
45	$(CH_3CO)_2N$	$2\text{-}CH_3C_6H_4NHSO_2$	168–170	52	$C_{15}H_{18}O_4N_4S$	51.42	51.42	5.17	5.18	15.99	16.09
46	H_2N	$2\text{-}CH_3OC_6H_4NHSO_2$	137–138, dec.	68	$C_{11}H_{14}O_3N_4S$	46.80	46.83	4.99	4.98	19.84	20.19
47	HCONH	$2\text{-}CH_3OC_6H_4NHSO_2$	169–170	34	$C_{12}H_{14}O_4N_4S$	46.44	46.58	4.55	4.69	18.05	18.27
48	H_2N	$2\text{-}ClC_6H_4NHSO_2$	155–156, dec.	63	$C_{10}H_{11}O_2N_4SCl$	41.88	42.04	3.87	3.93	19.54	19.69
49	$H_2N.HCl$	$2\text{-}ClC_6H_4NHSO_2$	162–163, dec.	81	$C_{10}H_{12}O_2N_4SCl_2$	37.15	37.14	3.74	3.88	17.34	17.45
50	CH_3CONH	$2\text{-}ClC_6H_4NHSO_2$	137–138	43	$C_{12}H_{13}O_3N_4SCl$	43.82	44.01	3.98	4.08	17.04	17.29
51	$(CH_3CO)_2N$	$2\text{-}ClC_6H_4NHSO_2$	181–183	60	$C_{14}H_{15}O_4N_4SCl$	45.34	45.19	4.07	4.07	15.11	15.28
52	H_2N	$1\text{-}C_{10}H_7NHSO_2$	169–170, dec.	36	$C_{14}H_{14}O_2N_4S$	55.61	55.71	4.67	4.69	18.53	18.69

[a] Compounds 24, 28, 31, 33, 36, 37, and 46 were recrystallized from ethanol with the use of Norite; 34, 38, 40, 43, 48, and 52 from ethanol; 49 from ethanol containing 1 or 2 drops of concd. hydrochloric acid; 29, 30, 35, 39, and 50 from water with the use of Norite; 27, 32, 41, 42, 44, 45, 47, and 51 from water; and 25 and 26 from methanol with the use of Norite.

Reaction Scheme B



Compound 10 was prepared in an analogous manner from 8 and methylamine.

1-Methyl-4-nitro-5-(phenylsulfamyl)imidazole (11) (and Compounds 14, 15, 16, and 17). 1-Methyl-4-nitro-5-(chlorosulfonyl)imidazole (8) (22.5 g., 0.1 mole) was added in small portions to 27.2 g. (0.3 mole) of aniline. The mixture was heated on a steam bath for 15 min., cooled, treated with 100 ml. of 2*N* hydrochloric acid, and the product was filtered.

Compounds 14, 15, and 16 were prepared in the same manner from 8 and the required amine. Compound 17 was obtained by the same process except that 0.1 mole of 8, 0.1 mole of 1-naphthylamine and 0.1 mole pyridine were employed.

1-Methyl-4-nitro-5-(dimethylsulfamyl)imidazole (12). Dimethylamine (18 g., 0.4 mole) was added to a stirred solution of 45 g. (0.2 mole) of 1-methyl-4-nitro-5-(chlorosulfonyl)-imidazole in 200 ml. of *p*-dioxane. The precipitated solid was filtered and discarded. The filtrate was evaporated to dryness in a stream of air and the residue was recrystallized.

1-Methyl-4-nitro-5-(dimethylaminomethylenesulfamyl)imidazole (13). A mixture of 20.6 g. (0.1 mole) of 1-methyl-4-nitro-5-sulfamylimidazole, 7.3 g. (0.1 mole) of *N*,*N*-dimethylformamide, 15.3 g. (0.1 mole) of phosphorus oxychloride, and 75 ml. of toluene was heated in an oil bath held at 110° for 2.5 hr. The toluene layer was decanted from the oily precipitate and the latter was dissolved in 600 ml. of hot water. The product separated when the solution was cooled.

1-Methyl-4-nitro-5-(piperidinomethylsulfamyl)imidazole (18). A mixture of 8.2 g. (0.04 mole) of 1-methyl-4-nitro-5-sulfamylimidazole, 3.2 ml. (0.04 mole) of formaldehyde solution (37%), 4 ml. (0.04 mole) of piperidine, and 20 ml. of water was stirred at room temperature for 15 min. The precipitate was filtered; m.p. 63–66°. This compound decomposed upon attempted purification by recrystallization from hot water. The analytical data indicated that the precipitate (m.p. 65–67°) obtained by cooling a saturated aqueous solution was not entirely pure.

1-Methyl-4-nitro-5-(morpholinomethylsulfamyl)imidazole (19). A mixture of 8.2 g. (0.04 mole) of 1-methyl-4-nitro-5-sulfamylimidazole, 3.2 ml. (0.04 mole) of formaldehyde solution (37%), 4 ml. (0.04 mole) of morpholine, and 30 ml. of water was stirred for several hours at room temperature and the product was filtered.

1-Methyl-4-nitro-5-(carbamylsulfamyl)imidazole (20). A mixture of 10.1 g. (0.049 mole) of 1-methyl-4-nitro-5-sulfamylimidazole, 4.2 g. (0.05 mole) of potassium cyanate, and 500 ml. of absolute ethanol was refluxed for 4 hr. The solid was filtered, dissolved in water, and the product was precipitated by acidification with acetic acid.

1-Methyl-4-nitro-5-(acetylsulfamyl)imidazole (21). A mixture of 20.6 g. of 1-methyl-4-nitro-5-sulfamylimidazole, 35 ml. of acetyl chloride, and 35 ml. of acetic acid was refluxed for 4 hr. The mixture was cooled and the product was filtered.

1-Methyl-4-nitro-5-(benzoylsulfamyl)imidazole (22). A mixture of 4 g. of 1-methyl-4-nitro-5-sulfamylimidazole, 3.5 ml. of benzoyl chloride, and 5 ml. of pyridine was heated on a steam bath for 5 hr. After 12 hr. at room temperature, the product was filtered.

5,5'-Dithiobis(1-methyl-4-nitroimidazole) (23). To a suspension of 10.0 g. of 1-methyl-4-nitro-5-mercaptoimidazole in 300 ml. of *p*-dioxane there was added 50 ml. of 3% hydrogen peroxide with occasional shaking. The solid dissolved after 15 min. and the solution became red in color. The mixture was diluted with 800 ml. of water, cooled, and the product was filtered.

1-Methyl-4-amino-5-mercaptoimidazole hydrochloride (24). 1-Methyl-4-nitro-5-mercaptoimidazole (2.7 g.) was dissolved in ammonia water and the solution was evaporated to dryness. Sodium hydrosulfite (15.0 g.) was added, gradually, to a stirred, aqueous solution of the ammonium salt dissolved in 100 ml. of water. The mixture was filtered and the filtrate was extracted with ether. Ethereal hydrogen chloride was added to the extract and the precipitated hydrochloride was filtered.

General procedure for the preparation of the amino compounds and their hydrochlorides (25, 26, 33, 34, 36, 37, 39, 40, 43, 46, 48, 49, and 52). A mixture of 0.04 mole of the nitro compound, dissolved in 150 ml. of *N*,*N*-dimethylformamide, and about 8 g. of wet Raney nickel[6] was hydrogenated under an initial pressure of 40–50 pounds until the calculated amount of hydrogen was absorbed (1–2 hr.). The mixture was filtered without suction and 5 ml. of concd. hydrochloric acid was added to the filtrate. The hydrochloride was obtained by removal of the solvent in a stream of air.

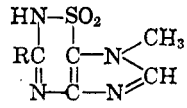
The free amine was prepared by neutralization of an aqueous solution of the crude hydrochloride with 8% aqueous sodium hydroxide and the precipitated amine was filtered.

1-Methyl-4-amino-5-(dimethylaminomethylsulfamyl)-imidazole (38). A solution of 2.6 g. of 1-methyl-4-nitro-5-(dimethylaminomethylenesulfamyl) imidazole in 120 ml. of *N*,*N*-dimethylformamide and 3 g. of wet Raney nickel was

(6) The nickel catalyst used in all experiments was Sponge Nickel Catalyst, preserved under water, purchased from Davision Chemical Co., Cincinnati 29, Ohio.

TABLE III

7-METHYL-6-THIA-1,6-DIHYDROPURINE 6,6-DIOXIDE AND DERIVATIVES



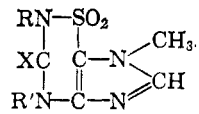
VIII

	R	M.P.	Yield, %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
VIIIa[a]	H	>340	52	$C_5H_6O_2N_4S$	32.96	32.39	3.31	3.65	30.75	30.75
VIIIb	CH_3	340–341, dec.	45	$C_6H_8O_2N_4S$	36.00	36.09	4.03	4.18	27.99	27.73
VIIIc	C_2H_5	296–297	56	$C_7H_{10}O_2N_4S$	39.25	39.20	4.70	4.73	26.15	26.16

[a] Compound VIIIa was recrystallized from water with the use of Norite; VIIIb and VIIIc from methanol with the use of Norite.

TABLE IV

7-METHYL-6-THIA-2-KETO- AND 7-METHYL-6-THIA-2-THIOKETO-1,2,3,6-TETRAHYDROPURINE 6,6-DIOXIDE AND DERIVATIVES



IX, X, XI, and XIII

	X	R	R'	M.P.	Yield, %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
IXa	O	H	H	226–228, dec.	86[a]	$C_5H_6O_3N_4S$[c]	29.70	29.78	2.99	3.08	27.70	27.78
IXb	S	H	H	227–228, dec.	23	$C_5H_6O_2N_4S_2$[d]	27.52	27.75	2.77	2.87	25.67	25.80
X	O	CH_3	CH_3	175–176	[b]	$C_7H_{10}O_3N_4S$	36.52	36.63	4.38	4.49	24.33	24.55
XI	O	H	CH_3	288–289, dec.	[b]	$C_6H_8O_3N_4S$	33.33	33.56	3.73	3.97	25.91	25.92
XIIIa	O	CH_3	H	243–244, dec.	17	$C_6H_8O_3N_4S$	33.33	33.37	3.73	3.73	25.91	26.00
XIIIb	S	CH_3	H	230–231, dec.	37	$C_6H_8O_2N_4S_2$[e]	31.02	31.15	3.47	3.47	24.12	24.23

[a] Crude yield. [b] 0.5 g. of X and 0.65 g. of XI were obtained from 3 g. of crude IXa. Compounds IXb, X, XI, and XIIIa were recrystallized from water; IXa from warm water; XIIIb from acetic acid. [c] Anal. Calcd.: S, 15.85. Found: S, 15.71. [d] Anal. Calcd.: S, 29.38. Found: S, 29.27. [e] *Anal.* Calcd.: S, 27.61. Found: S, 27.79.

hydrogenated under an initial pressure of 30 pounds until no more hydrogen was absorbed (3 hr.). After removal of the catalyst, the solvent was removed by distillation under reduced pressure in a nitrogen atmosphere. The residue was triturated with ethanol and then filtered.

Formyl derivatives (27, 35, 44, and 47). A mixture of 0.01 mole of the required amino compound and 5 ml. of anhydrous formic acid was heated on a steam bath for 1 hr. The mixture was poured onto crushed ice and the precipitate was filtered.

Monoacetyl (28, 41, and 50) *and butyryl* (29) *derivatives.* A mixture of 0.01 mole of the nitro compound, 200 ml. of absolute ethanol, and 3 g. of wet Raney nickel was hydrogenated under an initial pressure of 30 pounds until the calculated amount of hydrogen had been absorbed (2 hr.). The mixture was filtered and 15 ml. of acetic anhydride was added to the filtrate. After 24 hr., the solvent and excess acetic anhydride were removed under reduced pressure and the residue was recrystallized.

The butyryl derivative was prepared in the same manner except that butyric anhydride was used.

Diacetyl derivatives (42, 45, and 51). A mixture of 0.005 mole of the required amino compound, 4 ml. of acetic anhydride, and 2 ml. of pyridine was allowed to remain at room temperature for 12 hr. The precipitate was filtered.

1-Methyl-4-(diacetylamino)-5-(acetylsulfamyl)imidazole (32). A mixture of 0.88 g. of 1-methyl-4-amino-5-sulfamylimidazole, 3 ml. of acetic anhydride, and 10 ml. of pyridine was refluxed for 3 hr. After removal of the solvent, the residue was recrystallized.

The product was also obtained by heating a mixture of 3.5 g. of 1-methyl-4-amino-5-sulfamylimidazole and 6 ml. of acetic anhydride on a steam bath for 5 hr.

1-Methyl-4-(carbamylamino)-5-sulfamylimidazole (30). To a stirred solution of 8.4 g. of 1-methyl-4-amino-5-sulfamylimidazole hydrochloride in a minimum amount of water there was added an aqueous solution of 3.2 g. of potassium cyanate. After 3 hr., the precipitate was filtered and washed with water.

1-Methyl-4-(carbethoxyamino)-5-sulfamylimidazole (31). Ethyl chloroformate (3 ml.) was added, in small portions, to a stirred mixture of 3 g. of 1-methyl-4-amino-5-sulfamylimidazole and 6 ml. of pyridine, which was cooled in an ice bath. The mixture was stirred for 12 hr. at room temperature, diluted with 80 ml. of water, and cooled in an ice bath for several hours. The product was then filtered.

7-Methyl- (VIIIa), *2,7-dimethyl-* (VIIIb), *and 2-ethyl-7-methyl-6-thia-1,6-dihydropurine-6,6-dioxide* (VIIIc, Table III). A mixture of 0.01 mole of 1-methyl-4-amino-5-sulfamylimidazole (VII, 25) and 0.015 mole of freshly distilled ethyl orthoformate, ethyl orthoacetate, or ethyl orthopropionate was heated (about 30 min.) in an oil bath, maintained at 130–140°, until all of the alcohol produced had distilled. The product was filtered and recrystallized.

Compound VIIIa was obtained also by refluxing a mixture of 1.3 g. of VII and 4 ml. of anhydrous formic acid for 3 hr.

After the addition of ice water, the precipitate was filtered and recrystallized from water; m.p. > 340°; yield 0.1 g. (7%).

Anal. Calcd. for $C_5H_6O_2N_4S$: C, 32.92; H, 3.31; N, 30.75. Found: C, 32.50; H, 3.27; N, 30.40.

7-Methyl-6-thia-2-keto-1,2,3,6-tetrahydropurine-6,6-dioxide (IXa, Table IV). To a stirred solution of 8.8 g. of 1-methyl-4-amino-5-sulfamylimidazole (VII, 25) in 150 ml. of 4% aqueous sodium hydroxide there was added, dropwise, 70 ml. of 12.5% phosgene in benzene. Near the end of the addition, a solid began to separate and very small portions of 25% aqueous sodium hydroxide were added to dissolve the solid. The mixture was stirred for 4 hr., cooled, and made strongly acidic with concentrated hydrochloric acid. The precipitate was filtered, m.p. 225–227° dec.; yield 6.4 g. The filtrate, after the addition of more hydrochloric acid, was kept in a refrigerator whereupon an additional 2.3 g. of product precipitated, m.p. 226–228° dec.; total yield 8.7 g. (86%).

7-Methyl-6-thia-2-thioketo-1,2,3,6-tetrahydropurine-6,6-dioxide (IXb, Table IV). Thiophosgene (2.3 g.) was added to a stirred solution of 3.5 g. of 1-methyl-4-amino-5-sulfamylimidazole (VII, 25) in 46 ml. of 4% aqueous sodium hydroxide, cooled in an ice bath. The mixture was stirred for 4 hr. at room temperature. The precipitate was filtered (A) and washed with a small amount of 2*N* hydrochloric acid.

The filtrate (A) was cooled in an ice bath and made strongly acidic with concentrated hydrochloric acid; an additional amount of product precipitated.

1,3,7-Trimethyl- (X) *and 3,7-dimethyl-6-thia-2-keto-1,2,3,6-tetrahydropurine-6,6-dioxide* (XI, Table IV). To a stirred solution of 3 g. of 7-methyl-6-thia-2-keto-1,2,3,6-tetrahydropurine-6,6-dioxide (IXa) in 45 ml. of 5% aqueous sodium carbonate there was added 5.6 g. of methyl sulfate. After 1 hr., a solid began to separate and a small amount of saturated aqueous sodium carbonate solution was added to dissolve the solid. The mixture was stirred for 12 hr. and cooled in an ice bath for several hours. The precipitate (X) was filtered.

The filtrate was acidified with concentrated hydrochloric acid and kept in a refrigerator for 12 hr. The precipitate (XI) was filtered.

1,7-Dimethyl-6-thia-2-keto-1,2,3,6-tetrahydropurine-6,6-dioxide (XIIIa, Table IV). Phosgene (14 ml. of 12.5% phosgene in benzene) was added, dropwise, to a stirred solution of 1.9 g. of 1-methyl-4-amino-5-(methylsulfamyl)imidazole (XII, 33) in 25 ml. of 4% aqueous sodium hydroxide. A few drops of 25% aqueous sodium hydroxide solution were added, if necessary, to dissolve any precipitated solid. After 3 hr., the aqueous layer was separated, cooled, and made strongly acidic with concentrated hydrochloric acid. The precipitate was filtered.

1,7-Dimethyl-6-thia-2-thioketo-1,2,3,6-tetrahydropurine-6,6-dioxide (XIIIb, Table IV). To a stirred solution of 3.8 g. of 1-methyl-4-amino-5-(methylsulfamyl)imidazole (XII, 33) in 36 ml. of 4% aqueous sodium hydroxide solution, cooled in an ice bath, there was added 2.3 g. of thiophosgene. The mixture was stirred for 4 hr. at room temperature and the product was filtered.

ANN ARBOR, MICH.

[CONTRIBUTION FROM COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

1-Alkoxy-4-phenyl-4-propionoxypiperidines and Their 3-Methyl Homologs* as New Analgesics

RANDOLPH T. MAJOR AND FRIEDRICH DÜRSCH

Received August 1, 1960

α- and β-1-alkoxy-3-methyl-4-phenyl-4-propionoxypiperidines have been made and examined for analgesic action in rats. The β-isomers are much more active than the α-isomers. Several related compounds have been prepared. It was found that heating the 1-alkoxy-4-phenyl-4-hydroxypiperidines or their 3-methyl homologs with propionic anhydride did not result in acylation of the hydroxy group but in elimination of the 1-alkoxy group with formation of the *N*-acylated piperidine. A mechanism for this reaction is offered. The α- and β-1-alkoxy-3-methyl-4-phenyl-4-propionoxypiperidines were related stereochemically to the corresponding amines, alphaprodine and betaprodine.

Lee and his co workers[1] first prepared a series of 1-alkyl-3-methyl-4-aryl-4-propionoxypiperidine hydrochlorides some of which have strong analgesic action. One of this series, alphaprodine hydrochloride, 1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride, has found wide use as an analgesic in human medicine.[2]

In view of the similarities between the biological activities of some alkoxyamines and those of the related alkylamines[3] it was decided to synthesize some analogous compounds by replacing the *N*-alkyl group in the prodines of Lee with an *N*-alkoxy group.

The methods employed in the synthesis of the 1-alkoxy-4-phenyl-4-propionoxypiperidines and their 3-methyl homologs were similar to those used by Lee and co-workers[1] and are shown in Scheme A.

The required β-alkoxyamino esters, *N*-alkoxy-*N*-β-carbomethoxyethylamine (I), *N*-alkoxy-*N*-β-carbomethoxypropylamine (II), and *N*-alkoxy-*N*,*N*-bis(β-carbomethoxyethyl)amine (III) were prepared by the addition of alkoxyamines in methanol to methyl acrylate or methyl methacrylate, respectively. However, it was found that this reaction proceeds much slower than that described for

---

* Kindly supplied by Dr. J. Lee, Hoffmann-La Roche Inc., Nutley, N. J.

(1)(a) A. Ziering, L. Berger, S. D. Heinemann, and J. Lee, *J. Org. Chem.*, 12, 894 (1947); (b) L. Berger, A. Ziering, and J. Lee, *J. Org. Chem.*, 12, 904 (1947); (c) A. Ziering, and J. Lee, *J. Org. Chem.*, 12, 911 (1947); (d) A. Ziering, A. Motchane, and J. Lee, *J. Org. Chem.*, 22, 152 (1957).

(2) American Medical Association Council on Drugs, *New and Nonofficial Drugs*, J. B. Lippincott Co., Philadelphia, 1959, p. 313.

(3) L. W. Jones and R. T. Major, *J. Am. Chem. Soc.*, 49, 1527 (1927).