TABLE II

CHROMATOGRAPHIC ANALYSIS OF REDUCTION PRODUCTS

Pyrimidine	M.P., Crude HCl Salts	No.	R_f Values (23–26°) Ninhydrin				Iodine vapor				
2,4,6-Trichloro-		I	0.43[a]	0.18[a]			0.43[b]	0.29[c]			
2-Amino-	116–118	II					.49 (b)[b]	.27[d]	0.21(l)[c]		
2-Amino-4,6-dichloro-		III	.21 (f)[e]				.51 (h)[b]	.26[d]	.22(f)[d]		
4-Amino-		IV	.22[e]	.18[e]	0.14[e]	0.06[e]	.33(f)[d]	.20(l)[c]	.18[b]	0.13[b]	0.06[c]
4-Amino-2,6-dichloro-	146–147	V	.22[e]	.17[e]	.11[e]	.04[e]	.19(l)[c]	.14[b]	.04[c]		
5-Amino-		VI	.30[e]	.15[a]	.06(f)[e]		.20[c]	.16[c]	.11[c]	.06[c]	
5-Amino-4,6-dichloro-		VII	.35[d]	.19[f]			.33[d]	.25[c]	.19[b]		
5-Amino-2,4-dichloro-	187	VIII	.29(f)[e]	.18[e]	.12(f)[a]	.07[h]	.29[c]	.26[b]	.16[b]	.07[b]	
2,4-Dichloro-5-nitro-	178–180	IX	.35[f]	.19[g]	.14[e]	.11[e] 0.07[e]	.33[b]	.20[c]	.15[c]	.12[b]	.05[c]
4,6-Dichloro-5-nitro-			.17[a]	.12[a]	.05[a]		.30[b]	.21[d]	.13[b]		
4,6-Dichloro-2-methyl-	121–125	X	.49(f)[e]	.30[d]			.49(h)[b]	.29[d]			
2,6-Dichloro-4-methyl-	88–91	XI	.12[h]	.05[h]			.50(h)[b]	.31[d]	.14[c]	.06[c]	
2,4-Dichloro-5-methyl-	122–129	XII	.21[g]	.10(f)[a]	.07(f)[a]		.49(h)[b]	.27[d]	.14[c]		

Color of spots: [a] Light blue. [b] Dark brown. [c] Light brown. [d] Clear. [e] Yellow. [f] Dark purple. [g] Light purple. [h] Reddish purple. h = heavy, l = light, f = faint.

For chromatographic analysis[9,22] Whatman No. 4 paper was spotted with 0.1 *M* aqueous solutions. The spotted chromatograms were allowed to equilibrate for at least 16 hr. in the developing solvent vapor prior to development. The developing solvent was butanol–acetic acid–water (4:1:5 v./v. organic phase); the descending method being used. The chromatograms were dried, sprayed with ninhydrin solution, and placed in iodine vapor for spot detection.

Synthesis of Some 8-Substituted Bis(β-chloroethyl)amino Derivatives of Naturally Occurring *N*-Methylated Purines[1]

HENRY C. KOPPEL, ROBERT H. SPRINGER, ROLAND K. ROBINS, F. HOWARD SCHNEIDER, AND C. C. CHENG

Midwest Research Institute, Kansas City, Mo.

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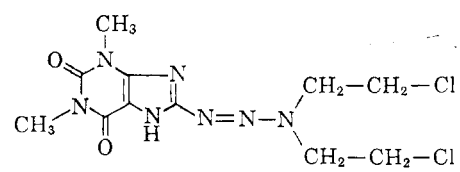
The derivatives of caffeine, theobromine, and theophylline containing a bis(β-chloroethyl)amino moiety attached either directly or through a methylene or an iminomethylidene group at the 8-position have been synthesized.

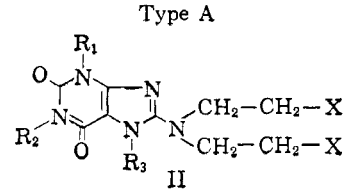
Recent indication of the activity of 8-[bis(β-chloroethyl)-triazeno]theophylline[2] (I) against a spontaneous tumor in experimental mice[3] encouraged a systematic synthetic study of certain derivatives of naturally occurring purine alkaloids related to I for further biological evaluations.



I

Three types of derivatives in this general area have been prepared in our laboratories: Type A compounds are those of which the nitrogen mustard moiety is attached directly to the 8-position of the purine ring (II. X = Cl). In Type B compounds the nitrogen mustard moiety is separated from the 8-position of the ring by a methylene bridge (III,

Type A



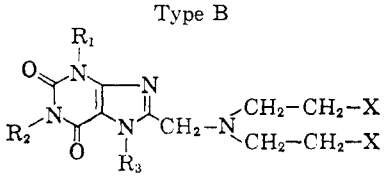
II

(1) This investigation was supported by research contract SA-43-ph-3025 from the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) G. A. Usbeck, J. W. Jones, and R. K. Robins, *J. Am. Chem. Soc.*, **83**, 1113 (1961).

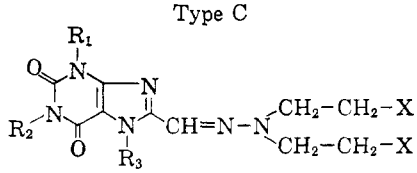
(3) Testing data to be published.

Type B



III

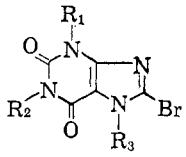
Type C



IV

X= Cl). The compounds of Type C are those with the nitrogen mustard function further separated from the 8- position by an iminoethylidene linkage (IV. X = Cl).

For the preparation of Type A compounds, 8-brominated purines (V) were used as the starting materials. 8-Bromocaffeine (V. R_1, R_2, R_3 = CH_3) was prepared by a known method,[4] 8-bromotheobromine (V. R_1, R_3 = CH_3, R_2 = H) was synthesized by a modification of Klosa's procedure for caffeine,[4] and 8-bromotheophylline (V. R_1, R_2 = CH_3, R_3 = H)[5] was obtained commercially.[6]

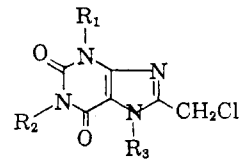


V

Treatment of V with diethanolamine in refluxing 2-ethoxyethanol gave the corresponding 8-[bis(β-hydroxyethyl)amino] derivatives (II. X = OH). The latter was then treated with thionyl chloride to yield the desired Type A compounds (II. X = Cl). Compounds of this type with the ring nitrogens unsubstituted have recently been synthesized by Chu, Harris, and Mautner.[7]

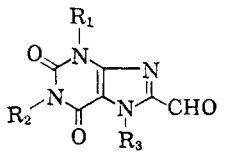
Hirschberg, Gellhorn, and Gump[8] have introduced a bis(β-chloroethyl)aminomethyl group to the "two" position of the benzimidazole ring system. The resulting compound, 2-[bis(β-chloroethyl)aminomethyl]benzimidazole has demonstrated some antitumor activity.[8,9] Consequently, Hirschberg *et al.*, and Ginzburg *et al.*, have independently synthesized 1-β-chloroethyl-2-[bis(β-chloroethyl)aminomethyl]benzimidazole,[8,10] Knobloch prepared 5-chloro- and 5,6-dichloro-2-[bis(β-chloroethyl)aminomethyl]-benzimidazole,[11] and Ginzburg and co-workers have prepared the corresponding 5,6-dimethyl derivative.[12] Since benzimidazole apparently acts as a purine antagonist in several biological systems,[8,13-15] the synthesis of Type B compounds is a logical approach to the search for compounds with better therapeutic indices.

The synthesis of 8-[bis(β-chloroethyl)aminomethyl]caffeine (III. R_1, R_2, R_3 = CH_3, X = Cl) was reported by Glushkov, Golovchinskaya, and Magidson.[16] Other compounds in the Type B series, 8-[bis(β-chloroethyl)-aminomethyl]theobromine (III. R_1, R_3 = CH_3, R_2 = H, X = Cl) and 8-[bis(β-chloroethyl)aminomethyl] theophylline (III. R_1, R_2 = CH_3, R_3 = H, X = Cl), were not known prior to the present study. Siegel[17] reported the preparation of 8-chloromethyltheobromine (VI. R_1, R_3 = CH_3, R_2 = H) and 8-chloromethyltheophylline (VI. R_1, R_2 = CH_3, R_3 = H). These derivatives were treated with diethanolamine to yield the corresponding 8-[bis(β-hydroxy-ethyl)-aminomethyl] derivatives (III. X = OH), which were readily converted to the desired theobromine and theophylline derivatives (III. X = Cl) by treatment with thionyl chloride.

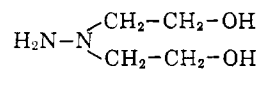


VI

The synthesis of Type C compounds requires the corresponding 8-purine aldehyde derivatives (VII) as the key intermediates. These aldehydes, prepared according to the method of Föhlisch,[18] were treated with *N*,*N*-[bis-(β-hydroxyethyl)]hydrazine



VII



VIII

(4) J. Klosa, *Arch. Pharm.*, **289**, 211 (1956).
(5) E. Fischer and L. Ach, *Ber.*, **28**, 3138 (1895).
(6) Aldrich Chemical Co., Milwaukee, Wis.
(7) S. H. Chu, J. E. Harris, and H. G. Mautner, *J. Org. Chem.*, **25**, 1759 (1960).
(8) E. Hirschberg, A. Gellhorn, and W. S. Gump, *Cancer Res.*, **17**, 904 (1957).
(9) J. E. Ullmann, H. G. Thompson, E. Hirschberg, J. Zaidenweber and A. Gellhorn, *Cancer Res.*, **19**, 719 (1959).
(10) O. F. Ginzburg, B. A. Porai-Koshits, M. I. Krylova, and S. M. Lotareichik, *Zhur. Obshchei Khim.*, **27**, 411 (1957).
(11) W. Knobloch, *Ber.*, **91**, 2557 (1958).
(12) O. F. Ginzburg, B. A. Porai-Koshits, M. I. Krylova, and K. Y. Mar'yanovskaya, *Khim. Nauka i prom.*, **4**, 548 (1959).
(13) L. S. Goodman, A. Gilman, and N. Hart, *Federation Proc.*, **2**, 80 (1943).
(14) D. W. Woolley, *J. Biol. Chem.*, **152**, 225 (1944).
(15) D. W. Woolley, Harvey Lectures, Series XLI, 189 (1945-1946).
(16) R. G. Glushkov, E. S. Golovchinskaya, and O. Y. Magidson, *J. Gen. Chem. U.S.S.R.*, **29**, 3700 (1959).
(17) E. Siegel Ph.D. dissertation, Technischen Hochschule Stuttgart, Germany, 1955.
(18) B. Föhlisch, Ph.D. dissertation, Technischen Hochschule Stuttgart, Germany, 1961.

TABLE I. 8-SUBSTITUTED BIS(β-CHLOROETHYL)AMINO DERIVATIVES OF *N*-METHYLATED PURINES

R_1	R_2	R_3	R_4	Formula	M.P.	Recrystallization Solvents	Calcd. C	Calcd. H	Calcd. N	Calcd. Cl	Found C	Found H	Found N	Found Cl
CH_3	H	CH_3	M[a]	$C_{11}H_{15}Cl_2N_5O_2$	250 d.[b]	Ethanol	41.2	4.7	21.8	22.2	40.9	4.7	21.4	22.2
CH_3	CH_3	H	M	$C_{11}H_{15}Cl_2N_5O_2$	186–188	Ethanol	41.2	4.7	21.8	22.2	41.4	4.9	22.0	22.0
CH_3	CH_3	CH_3	M	$C_{12}H_{17}Cl_2N_5O_2$	158–159	Ethanol–ether	43.1	5.1	20.9	21.2	42.8	5.1	20.7	21.3
CH_3	H	CH_3	CH_2M	$C_{12}H_{17}Cl_2N_5O_2$	179–181	Ethanol–water (3:2)	43.1	5.1	20.9	21.2	43.4	5.4	20.5	21.2
CH_3	CH_3	H	CH_2M	$C_{12}H_{17}Cl_2N_5O_2$	195–196	95% Ethanol	43.1	5.1	20.9	21.2	43.4	5.3	20.9	21.4
CH_3	H	CH_3	$CH=N-M$	$C_{12}H_{16}Cl_2N_6O_2 \cdot 1/2\ H_2O$	263–265	Acetic acid–ethoxyethanol	40.4	4.7	23.5	20.0	40.3	4.7	23.2	20.4
CH_3	CH_3	H	$CH=N-M$	$C_{12}H_{16}Cl_2N_6O_2$	205–207	Ethanol–water (2:1)	41.5	4.6	24.2	20.8	41.2	4.8	24.5	20.7
CH_3	CH_3	CH_3	$CH=N-M$	$C_{13}H_{18}Cl_2N_6O_2 \cdot HCl$	183–186	Ethanol–petroleum ether	40.0	5.0	21.2	26.8	40.2	4.8	21.4	27.2
										9.0[c]				8.8[c]

[a] M = $-N(CH_2CH_2Cl)(CH_2CH_2Cl)$. [b] Softened at 165°. [c] Ionizable chloride.

(VIII)[19] in acetic acid to give IV (X = OH). In the presence of a catalytic amount of pyridine, thionyl chloride converted these hydroxy derivatives (IV. X = OH) to the desired 8-[bis(β-chloroethyl)hydrazonemethylideno]purines (IV. X = Cl).

All the 8-substituted bis(β-chloroethyl)amino derivatives (see Table I) gave negative tests for ionizable chloride, with the exception of 8-[bis(β-chloroethyl)hydrazonomethylideno]caffeine (IV. R_1 R_2, R_3 = CH_3, X = Cl), which was isolated as a hydrochloride.

Type A compounds gave characteristic ultraviolet absorption spectra in absolute ethanol at 294 mμ (max). A hypsochromic shift to 275 mμ was characteristc of Type B compounds. Type C compounds produced two characteristic maxima in ethanol at 258 mμ and 335 mμ. The ultraviolet absorption spectra of the β-(hydroxyethyl)amino compounds in ethanol are strikingly similar to their corresponding chloro analogs.

The biological evaluation of these compounds is in progress.

Experimental[20]

8-[Bis(β-hydroxyethyl)amino]caffeine (II. R_1, R_2, R_3 = CH_3, X = OH).—A mixture of 60 g. of 8-bromocaffeine,[4] 60 g. of diethanolamine, and 500 ml. of 2-ethoxyethanol was refluxed for 18 hr. The resulting brown solution was evaporated under reduced pressure to a thick slurry, which was dissolved in 250 ml. of water. This aqueous solution was then extracted continuously with 500 ml. of chloroform for 6 hr. The chloroform extract was then distilled under reduced pressure and the residue recrystallized from benzene–ethanol to yield 60 g. of product, m.p. 125–126°.

Anal. Calcd. for $C_{12}H_{19}N_5O_4$: C, 48.7; H, 6.4; N, 23.6. Found: C, 48.8; H, 6.5; N, 23.6.

A Convenient Large Scale Preparation of 8-Bromotheobromine (V. R_1, R_3 = CH_3, R_2 = H).—To a stirred and refluxing suspension of 100 g. of theobromine in 300 g. of carbon tetrachloride and 700 g. of nitrobenzene was added dropwise 140 g. of bromine dissolved in 90 g. of nitrobenzene. After the addition was completed, the reaction mixture was refluxed with stirring for another 4 hr. The hot suspension was then carefully poured, with stirring, into 2 l. of acetone. The resulting white precipitate was filtered, washed with acetone and ether, and dried *in vacuo* to give 120 g. of 8-bromotheobromine which decomposed at 298°. This product is identical to that prepared by Lespagnol and Gaumeton[21] (d. 296°) who employed a high temperature, direct bromination method unsuitable for large scale preparation.

8-[Bis-(β-hydroxyethyl)amino]theobromine (II. R_1, R_3 = CH_3, R_2 = H, X = OH).—A mixture of 50 g. of 8-bromotheobromine and 50 g. of diethanolamine in 500 ml. of 2-ethoxyethanol was refluxed for 12 hr. The reaction mixture, which contained a small amount of insoluble material, was treated with charcoal and filtered. A white solid product was obtained after the filtrate was diluted with 500 ml. of acetone and chilled overnight. Recrystallization

(19) (a) L. Knorr and H. W. Brownsdon, *Ber.*, **35**, 4474 (1902). (b) M. Ishidate, Y. Sakurai, and Y. Kuwada, *Chem. Pharm. Bull.* (Japan), **8**, 543 (1960).

(20) All melting points were taken on the Thomas-Hoover melting point apparatus. The ultraviolet absorption spectra were determined on the Beckman DK-2 spectrophotometer.

(21) A. Lespagnol and A. Gaumeton, *Bull. soc. chim. France*, 253 (1961).

of the crude product from ethanol gave 48 g. of white crystals, m.p. 196–198°.

Anal. Calcd. for $C_{11}H_{17}N_5O_4$: C, 46.7; H, 6.0; N, 24.7. Found: C, 46.6; H, 6.4; N, 24.6.

8-[Bis(β-hydroxyethyl)amino]theophylline (II. R_1, R_2 = CH_3, R_3 = H, X = OH) was similarly prepared from 40 g. of 8-bromotheophylline[5,6] and 40 g. of diethanolamine in 500 ml. of 2-ethoxyethanol. Recrystallization from ethanol gave 34 g. of white crystals, m.p. 249–250°.

Anal. Calcd. for $C_{11}H_{17}N_5O_4$: C, 46.7; H, 6.0; N, 24.7. Found: C, 46.7; H, 5.8; N, 24.6.

8-[Bis(β-chloroethyl)amino]threobromine (II. R_1, R_2 = CH_3, R_3 = H, X = Cl) (See Table I).—To a mixture of 20 g. of 8-[bis(β-hydroxyethyl)amino]theobromine in 150 ml. of chloroform cooled in ice bath was added dropwise, with stirring, 100 ml. of thionyl chloride dissolved in 100 ml. of chloroform. After the addition had been completed, the mixture was refluxed for 30 min., during which time a clear solution was formed. Excess thionyl chloride and chloroform was then removed under reduced pressure. To the oily residue was added 150 ml. of absolute methanol. The solution was cooled in ice bath and crystallization took place shortly. The solid was filtered, washed with a small amount of cold methanol, ether, and recrystallized from ethanol. The yield was 12 g.

8-[Bis(β-chloroethyl)amino]theophylline (II. R_1, R_2 = CH_3, R_3 = H, X = Cl) was prepared by essentially the same method. Six grams of the product was obtained from 20 g. of 8-[bis(β-hydroxyethyl)amino]theophylline.

8-[Bis(β-chloroethyl)amino]caffeine (II. R_1, R_2, R_3 = CH_3, X = Cl) was prepared by a similar method except that 150 ml. of ice water rather than methanol was used to treat the oily residue resulting from the chlorination. Sixteen grams of the product was obtained from 20 g. of 8-[bis(β-hydroxyethyl)amino]caffeine.

A Convenient Large Scale Synthesis of 8-(Hydroxymethyl)caffeine.—To 96 ml. of 2 *N* sodium hydroxide solution was added 40 g. of 8-hydroxymethyltheobromine.[17] After complete solution was effected, the solution was diluted with water to 220 ml. and heated to 70°. To this solution, with stirring, was added 24 g. of dimethyl sulfate in 140 ml. of methanol. The pH of the reaction mixture was kept between 8 and 8.5 throughout the addition by the occasional addition of dilute sodium hydroxide. After the addition, the reaction solution was stirred for 30 min., and the methylation was complete as indicated by a constant pH (8–8.5). The solution was then extracted continuously with chloroform for 8 hr. The long, yellow needles, which slowly deposited from the chloroform extract, were collected and recrystallized from ethanol to give 26 g. of product as yellow needles, m.p. 225° (lit.,[16] m.p. 226°).

Anal. Calcd. for $C_9H_{12}N_4O_4$: N, 22.9. Found: N, 22.7.

8-[Bis(β-hydroxyethyl)aminomethyl]theobromine (III. R_1, R_3 = CH_3, R_2 = H, X = OH).—A mixture of 50 g. of 8-chloromethyltheobromine[17] and 50 g. of diethanolamine was stirred at room temperature. A slight exothermic reaction occurred, and there was an initial temperature rise to about 75°. After the initial temperature rise had subsided, the reaction mixture was heated at 100° for 15 min. with occasional stirring. The viscous slurry was then triturated with 300 ml. of absolute ethanol and the resulting precipitate was filtered and washed with acetone. Recrystallization of the crude product from 2-butanone gave 40 g. of white needles, m.p. 196–197°.

Anal. Calcd. for $C_{12}H_{19}N_5O_4$: C, 48.5; H, 6.4; N, 23.6. Found: C, 48.2; H, 6.5; N, 23.9.

8-[Bis(β-hydroxyethyl)aminomethyl]theophylline (III. R_1, R_2 = CH_3, R_3 = H, X = OH).—Forty-five grams of the desired product, m.p. 170–171°, was prepared from 60 g. of 8-chloromethyltheophylline[17] and 60 g. of diethanolamine by the same method described for the preparation of the theobromine analog.

Anal. Calcd. for $C_{12}H_{19}N_5O_4$: C, 48.5; H, 6.4; N, 23.6. Found: C, 48.3; H, 6.6; N, 23.5.

8-[Bis(β-chloroethyl)aminomethyl]theobromine (III. R_1, R_3 = CH_3, R_2 = H, X = Cl) (See Table I).—To a mixture of 25 g. of 8-[bis(β-hydroxyethyl)aminomethyl]theobromine and 400 ml. of dry chloroform cooled in an ice bath was added dropwise, with stirring, 125 ml. of thionyl chloride in 150 ml. of dry chloroform. After the addition was complete the mixture was refluxed for 3.5 hr. The excess thionyl chloride and chloroform were distilled under reduced pressure from the reaction mixture, which contained some yellow solid, and the residue was carefully treated with 250 ml. of ice water. The resulting solution, which contained a small amount of insoluble material, was treated with charocal and filtered. The filtrate was neutralized with saturated sodium carbonate solution. The precipitate, which formed during neutralization, was filtered and washed with ice water. Recrystallization from a mixture of 160 ml. of ethanol and 80 ml. of water gave 14 g. of pure product as white needles.

8-[Bis(β-chloroethyl)aminomethyl]theophylline (III. R_1, R_2 = CH_3, R_3 = H, X = Cl) was similarly prepared from 25 g. of 8-[bis(β-hydroxyethyl)aminomethyl]theophylline. The yield was 15 g. after recrystallization.

8-[Bis(β-hydroxyethyl)hydrazonomethylideno]theobromine (IV. R_1, R_3 = CH_3, R_2 = H, X = OH).—To 500 ml. of glacial acetic acid at 95° was added 41.6 g. of theobromine-8-aldehyde.[18] Forty-eight grams of bis(β-hydroxyethyl)-hydrazine[19] in 100 ml. of acetic acid was then added, with stirring, to this mixture all at once. The resulting yellow solution was stirred for 30 min. and its volume concentrated to 150 ml. It was then diluted with 500 ml. of acetone. The solid product, which crystallized gradually from the acetone solution was filtered and recrystallized from a mixture of methanol and water to yield 45 g. of white crystals, m.p. 261–263°.

Anal. Calcd. for $C_{12}H_{18}N_6O_4$: C, 46.4; H, 6.0; N, 27.1. Found: C, 46.2; H, 6.3; N, 27.0.

8-[Bis(β-hydroxyethyl)hydrazonomethylideno]theophylline (IV. R_1, R_2 = CH_3, R_3 = H, X = OH) was similarly prepared from 41.6 g. of theophylline-8-aldehyde.[18] Recrystallization of the product from a mixture of methanol and dimethylformamide gave 45 g. of white needles, m.p. 245–246°.

Anal. Calcd. for $C_{12}H_{18}N_6O_4$: C, 46.4; H, 6.0; N, 27.1. Found: C, 46.6; H, 6.3; N, 27.4.

8-[Bis(β-hydroxyethyl)hydrazonomethylideno]caffeine (IV. R_1, R_2 R_3 = CH_3, X = OH) was similarly prepared from 22 g. of caffeine-8-aldehyde.[18] Recrystallization from a mixture of ethanol and ether gave 23 g. of the product as white needles, m.p. 176–178°.

Anal. Calcd. for $C_{13}H_{20}N_6O_4$: C, 48.2; H, 6.2; N, 25.9. Found: C, 48.6; H, 6.4; N, 25.6.

8-[Bis(β-chloroethyl)hydrazonomethylideno]theophylline (IV. R_1, R_2 = CH_3, R_3 = H, X = Cl) (See Table I).—To 70 ml. of thionyl chloride containing 14 drops of dry pyridine was gradually added, with proper stirring and cooling, 14 g. of 8-[bis(β-hydroxyethyl)hydrazonomethylideno]theophylline. The resulting solution was refluxed for 20 min. after the addition was complete. To this solution was added, with stirring, 250 ml. of benzene. The yellow material which gradually crystallized was filtered and washed with benzene and ether. Recrystallization of the crude product twice from an ethanol water (2:1) mixture with the aid of charcoal gave 8 g. of white needles.

8-[Bis(β-chloroethyl)hydrazonomethylideno]theobromine (IV. R_1, R_3 = CH_3, R_2 = H, X = Cl) was similarly prepared from 15 g. of 8-[bis(β-hydroxyethyl)hydrazonomethylideno]-theobromine to give 12 g. of light yellow needles after recrystallization.

8-[Bis(β-chloroethyl)hydrazonomethylideno]caffeine (IV. R_1, R_2, R_3 = CH_3, X = Cl) was similarly prepared from 15 g. of the corresponding hydroxy derivative to give 9 g. of the desired product as white needles.

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2-Sulfobenzoic Acid Esters. II. 4-Amino Derivatives

BERNARD LOEV AND MINERVA KORMENDY

Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pa.

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An improved synthesis of 4-amino-2-sulfamylbenzoates (I) is described along with a number of substituted derivatives These compounds show marked anticonvulsant activity.

The preceding paper in this series[1] described the preparation of a series of sulfamylbenzoates, some of which possessed marked anticonvulsant activity. This activity[2] was initially discovered in a series of 4-amino-2-sulfamylbenzoates, and this paper describes improved methods of synthesis for these compounds (I) and their derivatives.

Hamor and Janfaza[3] synthesized I (R = CH_3, C_2H_5, and i-C_3H_7) by a sequence that involved the reaction of 6-nitrosaccharin with the appropriate alcohol followed by reduction of the resulting 4-nitro-2-sulfamylbenzoate. The 6-nitrosaccharin was prepared by the permanganate oxidation of 4-nitro-2-sulfamyltoluene. In our hand, the yields of 6-nitrosaccharin obtained from this oxidation step were quite low. In addition to this drawback, such a route restricted the variations in chemical structure that could be carried out. Attempts to improve the oxidation step by the use of manganese dioxide[4] or ammonium persulfate[5] as oxidizing agents were unsuccessful. In both cases the starting material was recovered unchanged. In attempts to prepare a more readily oxidized compound (ethyl 4-nitro-2-sulfocinnamate), ethyl *p*-nitrocinnamate was treated with fuming sulfuric or chlorosulfonic acids. At low temperature no sulfonation occurred; at higher temperatures decomposition resulted.

The nitration of saccharin was next considered as a means of eliminating the oxidation step. (Direct substitution reactions on saccharin have not been reported.) However, reaction of saccharin with nitric acid gave either no reaction or tars depending on the severity of conditions.

Syntheses based on the reaction sequence employed by Hamor were then abandoned, and an improved reaction sequence was developed related to the one previously described for the synthesis of unsubstituted sulfamylbenzoates. This sequence is rapid, facile, and gives high over-all yields. It also provides a large variety of structural modifications from a single intermediate (II).

The reaction sequence is outlined in Fig. 1. The yield in the oxidation and in the conversion of the resulting diacid to the dichloride (II) is 60 to 80% in each step. The reaction of the dichloride with aliphatic alcohols gives only the carboxylic ester, III. (Attempts to synthesize aromatic esters led to anomalous results which will be described in Part III of this series.) There was no evidence of sulfonic ester formation, even when an excess of alcohol was used. Compound IV (R = isopropyl) was found to exist in polymorphic forms, m.p. 128–130° and 153–154°. The three steps from the phosphorus pentachloride reaction through to the isolation of IV, can be carried out without isolation or purification of the intermediates, and over-all yields in this sequence often approach 80%.

Catalytic reduction of IV proceeded in high yield. However, in connection with other work, a study of the action of various chemical reducing agents on IV was made. Of the following reduction systems—stannous chloride in acetic acid, stannous chloride and hydrochloric acid in isopropyl alcohol, ferrous hydroxide in aqueous or isopropyl alcoholic solution, zinc and calcium chloride in ethanol, titanium trichloride or sodium hydrosulfite in ethanol, and sodium hydrosulfite in aqueous pyridine—only the hydrosulfite–pyridine procedure was successful (60% yield).

The sulfamyl *N*-alkyl or aryl substituted derivatives were prepared by substituting the appropriate amine for ammonia in the reaction with III. When III (R = isopropyl) was treated with hydrazine, the sulfamyl *N*-amino derivative (a sulfonhydrazide, Table I, compound 10) was ob-

(1) B. Loev and M. Kormendy, Part I, *J. Org. Chem.*, **27**, 1703 (1962).

(2) We are indebted to Dr. A. Kandel and co-workers for carrying out the pharmacological examination of these compounds. A detailed presentation of their results will be published elsewhere.

(3) G. H. Hamor and M. Janfaza. Thesis of M. Janfaza, 1957, School of Pharmacy, University of Southern California. These, and certain related compounds, were made available to us for pharmacological testing by Dr. Hamor.

(4) I. K. Fel'dman *et al.*, *J. Gen. Chem., USSR*, **15**, 962 (1945); *Chem. Abstr.*, **40**, 6443 (1946).

(5) C. Beck, German Patent 80.165 (1894).