H_2O. On cooling, a solid appeared which was filtered to give 36 g of amber crystals, mp 150–153°. *Anal.* ($C_{14}H_{12}N_2O$) C, H, N.

2-Aminomethyldiphenylamine.—To a hot stirred suspension of 15 g of $LiAlH_4$ in 200 ml of dioxane under N_2 was added 31 g of N-phenylanthranilamide in 200 ml of dioxane. After addition, the suspension was stirred and refluxed for 18 hr. Decomposition by successive addition of 15 ml of H_2O, 15 ml of 15% aqueous NaOH, and 45 ml of H_2O, filtration, and evaporation of the dioxane gave a colorless oil, bp 140–160° (0.1 mm) (20.1 g). This compound was used without further purification in the next step.

N-Phenylanthranilamide.—To a stirred suspension of 36.8 g of N-phenylisatoic anhydride in 200 ml of EtOH was added 50 ml of 28% aqueous NH_3 dropwise. After addition, the solution was refluxed for 0.5 hr and cooled. Addition of H_2O gave 31.0 g of white crystals. Recrystallization from EtOH–H_2O gave crystals, mp 117–123°. *Anal.* ($C_{13}H_{12}N_2O$) C, H, N.

N-Phenylisatoic Anhydride.—To a solution of 25.0 g of N-phenylisatin in 600 ml of AcOH was added 150 ml of 40% AcO_2H. After stirring for 3 days at room temperature the solution was poured into H_2O and filtered, and the solid was recrystallized (C_6H_6) to give 14.9 g of light amber crystals, mp 174–177°. *Anal.* ($C_{14}H_{19}NO_3$) C, H, N.

2-Methylaminobenzamide.—To a stirred suspension of 50 g of N-methylisatoic anhydride in 200 ml of EtOH was added dropwise 50 ml of 28% aqueous NH_3. After addition, the solution was heated on a steam bath for 2 hr. On cooling, a solid formed to give 31 g of colorless crystals, mp 158–161°. This compound was used without further purification in the next step.

2-Methylaminobenzylamine.—To a hot stirred suspension of 15 g of $LiAlH_4$ in 200 ml of dioxane was added dropwise a hot solution of 31 g of 2-methylaminobenzamide in 300 ml of dioxane. The reaction was refluxed for 18 hr and decomposed by successive addition of 15 ml of H_2O in 15 ml of dioxane, 15 ml of 15% aqueous NaOH solution, and 45 ml of H_2O. Filtration and evaporation of the solvent gave a colorless oil, bp 88–96° (0.15 mm) (22.6 g). *Anal.* ($C_{18}H_{12}N_2$) C, H, N.

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Notes

Synthesis of Potential Antimalarial Agents. I.[1] 6- and 6,9-Disubstituted Purines

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The mode of action of chloroquine and related antimalarial compounds is thought to be primarily the inhibition of the enzymatic synthesis of DNA.[2] The activity of chloroquine in the mouse is attributed to the 25-fold greater accumulation of the drug in parasitized (*Plasmodium berghei*) than in nonparasitized erythrocytes.[2] A number of antimetabolites such as purine-6(1H)-thione are also known to interfere with nucleic acid biosynthesis,[3] but apparently have no antimalarial activity.[4] Although the association of purine-6(1H)-thione with rat RNA might be one mode by which this compound interferes with cellular metabolism,[5] the lack of antimalarial activity of this and related compounds might be due to the lack of selective uptake or binding with parasitized erythrocytes. Derivatives of the cytotoxic purines that might concentrate selectively in parasitized erythrocytes were prepared by the attachment of well-known antimalarial side changes.

This study included the preparation of both 6-substituted and 6,9-disubstituted purines, the yields and properties of which are listed in Table I. Reaction of a 6-chloropurine with amines containing antimalarial side chains gave the 6-N-substituted adenines **1–10**, **18–25**, **33–36**, and **44**. The reaction conditions are given in Table I, and typical procedures are given in the Experimental Section.[6–10] The 6-chloropurines containing an antimalarial side chain in the 9 position of the ring were prepared in two steps from 5-amino-4,6-dichloropyrimidine.[11,12] Standard procedures were used to convert these 6-chloropurines to the 9-substituted purine analogs listed in Table I.

The 49 compounds prepared in this study, 7- and 9-benzyl-6-(*p*-chloroanilino)-9H-purine, ethyl 9-(6-*p*-chloroanilino)-9H-purineacetate, and 6-methylthio-9-β-D-ribofuranosyl-9H-purine were submitted for evaluation against mice infected with a lethal dose of *P. berghei*.[13] Although screening results are incomplete, no significant activity has yet been observed.

(1) This work was carried out for the Division of Medicinal Chemistry, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, under Contract No. DA-49-193-MD-2999. This is Contribution No. 409 from the Army Research Program on Malaria.

(2) (a) F. E. Hahn, R. L. O'Brien, J. Ciak, J. L. Allison, and J. G. Olenick, *Military Med.*, **131** (Suppl), 1071 (1966); (b) P. B. Macomber, R. L. O'Brien, and F. E. Hahn, *Science*, **152**, 1374 (1966).

(3) For a review of this subject, see J. A. Montgomery, *Progr. Drug Res.*, **8**, 433 (1965).

(4) No reference was found in the literature to antimalarial activity of these compounds, and the conclusion that they possess no antimalarial activity was confirmed by Dr. T. R. Sweeney.

(5) H. J. Hansen and S. B. Nadler, *Proc. Soc. Exp. Biol. Med.*, **107**, 324 (1961).

(6) For the preparation of *p*-(2-aminoethyl)benzenesulfonamide, see E. Miller, J. M. Sprague, L. W. Kissinger, and L. F. McBurney, *J. Amer. Chem. Soc.*, **62**, 2099 (1940).

(7) We wish to thank Eastman Chemical Products, Inc., for a sample of 5-amino-2,2-dimethylpentanol.

(8) For the preparation of 4-amino-α-diethylamino-*o*-cresol, see J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb, and A. L. Rawlins, *J. Amer. Chem. Soc.*, **70**, 1363 (1948).

(9) Acid hydrolysis of 4-acetamido-2,6-bis(1-pyrrolidinylmethyl)phenol gave 4-amino-2,6-bis(1-pyrrolidinylmethyl)phenol; see ref 8.

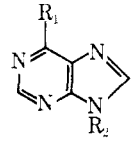
(10) For the preparation of *p*-amino-N,N′-bis(2-methoxyethyl)benzamidine, see H. V. Peckmann, *Ber.*, **30**, 1779 (1897).

(11) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Med. Pharm. Chem.*, **5**, 866 (1962).

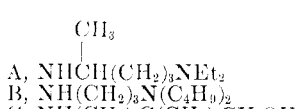
(12) J. A. Montgomery and C. Temple, Jr., *J. Amer. Chem. Soc.*, **80**, 409 (1958).

(13) For a description of the test procedure, see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

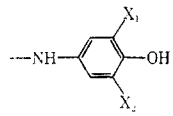
TABLE I
6- AND 6,9-DISUBSTITUTED PURINES



Antimalarial Side Chain (R_1)



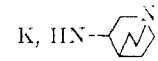
A, $NHCH(CH_3)(CH_2)_3NEt_2$
B, $NH(CH_2)_3N(C_4H_9)_2$
C, $NH(CH_2)_3C(CH_3)_2CH_2OH$



D, $X_1 = H$; $X_2 = CH_2NEt_2$
E, $X_1 = X_2 = CH_2N$(pyrrolidine)

F, $NHCH_2C_6H_4SO_2NH_2$-*p*
G, $NHCH_2CH_2C_6H_4SO_2NH_2$-*p*

J, $NHCH_2CHCH_2NEt_2$

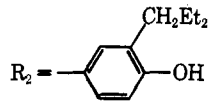


K, HN-(imidazole)
L, NHC_6H_4Cl-*p*
M, *p*-$NHC_6H_4CNH(CH_2)_2OCH_3$

Compd	Method	Reaction: Time, hr	Reaction: Temp, °C	Recrystn[a] solvent	Yield, %	Mp,[b] °C	Formula	Analyses
				R_2 = H				
1, R_1 = A	A-2	24	100	A + B	37	120–124[c]	$C_{14}H_{24}N_6 \cdot 2HCl$[d]	C, H, Cl, N
2, R_1 = B	A-2	12	88	C	73	198–199	$C_{16}H_{28}N_6 \cdot HCl$	C, H, Cl, N
3, R_1 = C	B-2	5	97	D[e]	91	187–188[f]	$C_{12}H_{19}N_5O$	C, H, N
4, R_1 = D	C-2	9	100	A[g]	54	202–204[h]	$C_{18}H_{20}N_6O \cdot 2HCl$[d]	C, H, Cl, N
5, R_1 = E	C-2	3	100	D[e]	28	212–214[f]	$C_{21}H_{27}N_5O \cdot 3HCl$[i]	C, H, Cl, N
6, R_1 = F	B-3	5	78	E	57	279–280[f,j]	$C_{12}H_{12}N_6O_2S$	C, H, N, S
7, R_1 = G	B-3	10	78	E	67	242–243	$C_{13}H_{14}N_6O_2S$	C, H, N, S
8, R_1 = J	A-2	12	100	C[e,g]	37	203–205[f]	$C_{12}H_{20}N_6O \cdot 2HCl$	C, H, Cl, N
9, R_1 = K	B-3	5	78	A[e]	55	198[k]	$C_{12}H_{16}N_6 \cdot HCl$	C, H, Cl, N
10, R_1 = M	C-1	6	97	F[e]	62	212–213	$C_{18}H_{25}N_7O_2 \cdot 2HCl$	C, H, Cl, N
				R_2 = $CH_3CH(CH_2)_3NEt_2$				
11, R_1 = Cl	D + F	20	...[l,m]	A + G[g]	71	159–160	$C_{14}H_{22}ClN_5 \cdot HCl$[d]	C, H, Cl, N
12, R_1 = H	...[n]	0.5	...[m]	B[e]	86	127–130[f]	$C_{14}H_{23}N_5 \cdot HCl$	C, H, Cl, N
13, R_1 = OH	...[n]	5	118	B[e]	97	98[f]	$C_{14}H_{23}N_5O \cdot 1.5HCl$[i]	C, H, Cl, N
14, R_1 = NH_2	...[n]	16	120	D[g]	76	181–183[c]	$C_{14}H_{24}N_6 \cdot HCl$	C, H, Cl, N
15, R_1 = $NHNH_2$	...[n]	2	78	B + C	31	...[o]	$C_{14}H_{25}N_7 \cdot 2HCl$	C, H, Cl, N
16, R_1 = SH	...[n]	2	78	C	39	239[h]	$C_{14}H_{23}N_5S$	C, H, N, S
17, R_1 = SMe	...[n]	20	...[m]	C + H[p]	68	119–121[f]	$C_{15}H_{25}N_5S \cdot HCl$	C, H, Cl, N
18, R_1 = A	A-1	6	100	B[e,g]	71	...[o]	$C_{23}H_{43}N_7 \cdot 2HCl$[d]	C, H, Cl; N[q]
19, R_1 = B	A-1	6	100	I + J	76	...[o]	$C_{25}H_{47}N_7 \cdot 3HCl$	C, H, Cl, N
20, R_1 = C	B-2	3	97	B + D	86	168–170	$C_{21}H_{38}N_6O \cdot 2HCl$[d]	C, H, Cl, N
21, R_1 = D	C-2	3	100	D	49	190–192[h]	$C_{25}H_{39}N_7O \cdot 3HCl$[r]	C, H, Cl, N
22, R_1 = F	B-2	8	97	C	80	135–138[f]	$C_{21}H_{31}N_7O_2S \cdot 2HCl$[i]	C, H, Cl, N
23, R_1 = G	B-2	8	97	C[e]	95	248–250[f]	$C_{22}H_{33}N_7O_2S \cdot 2HCl$	C, H, Cl, N
24, R_1 = J	A-1	6	100	B[e,g]	45	...[o]	$C_{21}H_{33}N_7O \cdot 3HCl$[r]	C, H, Cl, N
25, R_1 = L	B-1	2	97	C	52	228–230	$C_{20}H_{27}N_6 \cdot 2HCl$	C, H, Cl, N
				R_2 = $CH_2C_6H_4SO_2NH_2$-*p*				
26, R_1 = Cl	D + G	3[l]	75	E	67	207[h]	$C_{12}H_{10}ClN_5O_2S$	C, H, Cl, N
27, R_1 = H	...[n]	0.75	...[m]	E[e]	81	240–242	$C_{12}H_{11}N_5O_2S$	C, H, N, S
28, R_1 = OH	...[n]	4	118	E	69	320–322[f,j]	$C_{12}H_{11}N_5O_3S$	C, H, N, S
29, R_1 = NH_2	...[n]	16	120	E	64	293–294[f]	$C_{12}H_{12}N_6O_2S$	C, H, N, S
30, R_1 = $NHNH_2$	...[n]	3	78	A[e]	91	224–226[f]	$C_{12}H_{13}N_7O_2S \cdot HCl$	C, H, Cl, N
31, R_1 = SH	...[n]	2	78	K[g]	90	291–292[f,j]	$C_{12}H_{11}N_5O_2S_2$	C, H, N, S
32, R_1 = SMe	...[n]	24	...[m]	E[e]	97	220–222	$C_{13}H_{13}N_5O_2S_2$	C, H, N, S
33, R_1 = A	B-2	10	97	C	61	...[s]	$C_{21}H_{31}N_7O_2S \cdot 2HCl$	C, H, Cl, N
34, R_1 = F	B-3	6	78	A[e]	71	286–288[t]	$C_{19}H_{19}N_7O_4S_2$	C, H, N, S
35, R_1 = J	A-1	3	100	C[e,g]	74	213–215[f]	$C_{19}H_{27}N_7O_3S \cdot 2HCl$	C, H, Cl, N
36, R_1 = L	B-1	2	97	A[e]	82	287–289[f,j]	$C_{18}H_{15}ClN_6O_2S \cdot HCl$	C, H, Cl, N
				R_2 = $-CH_2CH(OH)CH_2NEt_2$				
37, R_1 = Cl	D + F	72	...[l,m]	D	65	224–226[f]	$C_{12}H_{18}ClN_5O \cdot HCl$	C, H, Cl, N
38, R_1 = H	...[n]	0.5	...[m]	B[e,p]	71	135–137	$C_{12}H_{19}N_5O \cdot HCl$	C, H, N
39, R_1 = NH_2	...[n]	16	120	A[e]	64	204–206[f]	$C_{12}H_{20}N_6O \cdot HCl$	C, H, Cl, N
40, R_1 = $NHNH_2$	...[n]	3	78	A	35	209–211[f]	$C_{12}H_{21}N_7O \cdot 2HCl$	C, H, Cl, N
41, R_1 = $^+NMe_3Cl^-$	...[n]	5	...[m]	J[e]	77	98–100[f]	$C_{15}H_{27}ClN_6O$	C, H, Cl, N
42, R_1 = SH	...[n]	2	78	J + L[g]	85	271–273[f,j]	$C_{12}H_{19}N_5OS \cdot HCl$	C, H, Cl, N
43, R_1 = SMe	...[n]	24	...[m]	E[e,g]	63	84–85	$C_{13}H_{21}N_5OS$	C, N, S; H[u]
44, R_1 = L	B-1	2	97	A[e]	77	231–233[f]	$C_{18}H_{28}ClN_6O \cdot 2HCl$	C, H, Cl, N
				R_2 = C_6H_4OH-*p*				
45, R_1 = Cl	E + G	64	...[l,m]	M	78	>300	$C_{13}H_7ClN_4O$	C, H, Cl, N

TABLE I (*Continued*)

Compd	Method	Reaction: Time, hr	Reaction: Temp, °C	Recrystn[a] solvent	Yield, %	Mp,[b] °C	Formula	Analyses
46, R_1 = Cl	E + G	64	...[l,m]	A	88	235–237[f,i]	$C_{16}H_{18}ClN_5O \cdot HCl$	C, H, N
47, R_1 = SH	...[n]	2	78	A[e]	29	...[o]	$C_{16}H_{19}N_5OS \cdot 1.5HCl$[d]	C, H, N, S



[a] A, EtOH; B, EtOAc; C, *i*-PrOH; D, MeCN; E, H_2O; F, *n*-PrOH; G, THF; H, petroleum ether (bp 85–105°); I, $CHCl_3$; J, Et_2O; K, precipitated from a basic solution with glacial acetic acid; L, MeOH; M, dioxane. [b] Melting points were determined in capillary tubes in a stirred oil bath unless otherwise indicated. [c] Presoftening. [d] $0.5H_2O$. [e] Trituration. [f] Decomposition. [g] Dried at 78° *in vacuo* over P_2O_5. [h] Kofler Heizbank apparatus. [i] H_2O. [j] Mel-Temp apparatus. [k] Decomposition slowly from 198°. [l] See Experimental Section. [m] Room temperature. [n] See Discussion. [o] Indefinite. [p] Dried at 56° *in vacuo* over P_2O_5. [q] N: calcd, 19.63; found, 19.18. [r] $2H_2O$. [s] Decomposition from 108°. [t] H: calcd, 7.17; found, 6.76.

Experimental Section[14]

Aminodechlorination Reactions.—The conditions for the preparation of the N-substituted adenines listed in Table I are given, followed by a specific example.

Method A.—Mixtures of the appropriate 6-chloropurine in H_2O containing either 1.5 equiv of amine A-1 or 2 equiv of amine A-2 were refluxed.

6-(4-Diethylamino-1-methylbutylamino)purine Dihydrochloride Hemihydrate (1).—A solution of 6-chloropurine (3.09 g, 20.0 mmoles) and 2-amino-5-diethylaminopentane (6.37 g, 40.0 mmoles) in H_2O (75 ml) was heated at reflux for 24 hr. The solution was treated with Norit, filtered through Celite, and evaporated to dryness. This residue was repeatedly dissolved in EtOH and evaporated to dryness to remove H_2O. The product was then separated from most of the accompanying 2-amino-5-diethylaminopentane hydrochloride (2.85 g) by extraction with Et_2O (400 ml). The residue from the Et_2O extract was dissolved in H_2O containing 1 *N* NaOH (40 ml), and the remainder of the amine impurity was extracted with $CHCl_3$ (five 25-ml portions). The aqueous solution was neutralized with 1 *N* HCl (40 ml), evaporated to dryness under reduced pressure, and the resulting residue was dried azeotropically with EtOH. The residue was then extracted with MeCN (five 25-ml portions), the combined extracts were evaporated to dryness, and the solid was recrystallized (4:1 EtOH–EtOAc); yield 2.07 g.

Method B.—Equivalent amounts of the 6-chloropurine and amine were refluxed in *n*-PrOH (B-1), *n*-PrOH containing an equivalent amount of $NaHCO_3$ (B-2), or EtOH containing a three- to fourfold excess of Et_3N (B-3).

α-(Purin-6-ylamino)-*p*-toluenesulfonamide (6).—A solution of 6-chloropurine (4.0 g, 26 mmoles), *p*-aminomethylbenzenesulfonamide hydrochloride (5.8 g, 26 mmoles), and Et_3N (7.9 g, 78 mmoles) in EtOH (50 ml) was heated at reflux for 5 hr. After cooling the yellow solid was collected by filtration, washed with EtOH (three 25-ml portions), and recrystallized (H_2O, 1900 ml); yield 4.5 g.

Method C.—Equivalent amounts of the 6-chloropurine and amine·2HCl were refluxed in *n*-PrOH (C-1) or H_2O (C-2).

α-(Diethylamino)-4-(purin-6-ylamino)-*o*-cresol Dihydrochloride Hemihydrate (4).—A solution of 6-chloropurine (2.32 g, 15.0 mmoles) and 4-amino-α-diethylamino-*o*-cresol dihydrochloride (4.40 g, 16.5 mmoles) in H_2O (100 ml) was heated at reflux for 9 hr. The hot solution was treated with Norit, filtered through Celite, and evaporated to dryness under reduced pressure. The oily residue solidified after being repeatedly dissolved in EtOH, followed by evaporation to dryness *in vacuo*. The resulting solid was washed with EtOH (50 ml), then recrystallized (EtOH); yield 3.16 g.

4-Alkylamino-5-amino-6-chloropyrimidines. Method D. α-[(5-Amino-6-chloro-4-pyrimidinyl)amino]-*p*-toluenesulfonamide.—A mixture of 5-amino-4,6-dichloropyrimidine (24.6 g, 150 mmoles), *p*-aminomethylbenzenesulfonamide hydrochloride (36.7 g, 165 mmoles), and $NaHCO_3$ (27.8 g, 332 mmoles) in 2-(2-methoxyethoxy)ethanol (150 ml) was stirred and heated at 150° for 5 hr. The resulting mixture was dried on an aspirator for 0.5 hr at 80° and filtered to remove inorganic salts. The filtrate was evaporated to dryness and the residue was dried for 2 hr at 80° *in vacuo*. The solid residue was triturated in EtOH (two 250-ml portions), and the pale yellow solid was collected by filtration and dried at room temperature *in vacuo* over P_5O_2; yield 33.8 g (72%). A portion of the product (3.0 g) was recrystallized (MeCN, 300 ml); yield 2.1 g, mp 244–246°. *Anal.* ($C_{11}H_{12}ClN_5O_2S$) C, H, Cl, N, S.

In the preparation of crude 5-amino-6-chloro-4-[3-(diethylamino)-2-hydroxypropyl]aminopyrimidine, the reactants were refluxed for 6 hr in *n*-BuOH.

Method E. *p*-[(5-Amino-4-chloro-6-pyrimidinyl)amino]phenol Hydrochloride.—A solution of *p*-aminophenol hydrochloride (1.9 g, 13 mmoles) and 5-amino-4,6-dichloropyrimidine (1.6 g, 10 mmoles) in H_2O (26 ml), EtOH (4 ml), and concentrated HCl (0.4 ml) was heated at reflux for 8 hr. The resulting solution was diluted with H_2O (20 ml) and chilled. The solid that precipitated was collected by filtration and dried at room temperature *in vacuo* over P_2O_5; yield 2.5 g (91%); decomposed without melting from 220°. *Anal.* ($C_{10}H_9ClN_4O \cdot HCl$) C, H, N.

9-Alkyl-6-chloro-9H-purines. Method F. 6-Chloro-9-(4-diethylamino-1-methylbutyl)-9H-purine (11).—The crude, oily residue of 5-amino-6-chloro-4-[(4-diethylamino-1-methylbutyl)-amino]pyrimidine (114 g), obtained from 57.4 g of 5-amino-4,6-dichloropyrimidine, was dissolved in 500 ml of ethyl orthoformate, and 29.2 ml of concentrated HCl was added portionwise with cooling. The resulting mixture was stirred at room temperature for 20 hr and filtered, and the filtrate was evaporated under reduced pressure to approximately two-thirds of the original volume. The product that precipitated was collected by filtration and triturated with THF and then with Et_2O and dried *in vacuo* over P_2O_5; yield 77.7 g. An additional amount of crude product was obtained by evaporation of the reaction mixture to dryness and trituration of the residue with THF; yield 18.3 g of a brown solid, mp 141–144°. This sample was recrystallized (1:3 EtOH–THF, 700 ml); yield 7.50 g, mp 159–160°. This sample did not lose its water of hydration when it was dried *in vacuo* (P_2O_5) at 78°. The total yield was 85.2 g.

The free base was obtained by dissolving 1.4 g (4.1 mmoles) of the salt in a minimum amount of H_2O and treating the solution with 4.2 ml of 1.0 *N* NaOH. The oil that separated was extracted with five 20-ml portions of Et_2O, and the combined extracts were washed with three 5-ml portions of H_2O and dried ($MgSO_4$). The Et_2O was evaporated to dryness, and the pale yellow oil was dried *in vacuo* (P_2O_5); yield 1.1 g (91% recovery). *Anal.* ($C_{14}H_{22}ClN_5$) C, H, Cl, N.

Method G. α-[(6-Chloropurin-9-yl)-9H-*p*-toluenesulfonamide (26).—A suspension of α-[(5-amino-6-chloro-4-pyrimidinyl)amino]-*p*-toluenesulfonamide (7.8 g, 25 mmoles) in diethoxymethyl acetate (75 ml) was stirred at room temperature for 64 hr, and the resulting solution was heated at 75° for 3 hr and evaporated to dryness *in vacuo*. This residue was stirred at room temperature in 0.2 *N* HCl (125 ml), and the solid that deposited was collected by filtration and recrystallized (H_2O); yield 5.4 g.

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(14) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.