Heterocyclic Systems with a Bridgehead Nitrogen. II.[1] 6-Chloroimidazo[2,1-b]thiazole and Some of Its 5-Substituted Derivatives[2]

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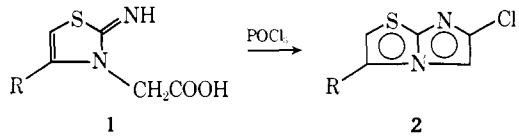
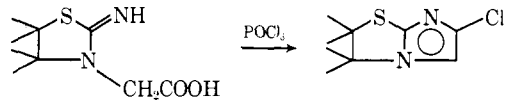
The reaction of 3-carboxymethyl-2-iminothiazoline and $POCl_3$ gives 6-chloroimidazo[2,1-*b*]thiazole. This system undergoes electrophilic substitution at the 5 position, as shown by means of nmr analysis. Some of these compounds demonstrated antiinflammatory and antihypertensive activity.

The formation of an imidazo[2,1-*b*]thiazole from a preformed thiazole usually is accomplished by treatment of a 2-aminothiazo lederivative with an α-halo ketone. Such reactions give 6-alkyl and 6-aryl derivatives.[3-5] We wish to report a new procedure for the synthesis of chloro-substituted imidazo[2,1-*b*]thiazoles commencing with a thiazole nucleus. The reaction of 3-carboxymethyl-2-iminothiazoline (**1a**)[6] and $POCl_3$ gives directly 6-chloroimidazo[2,1-*b*]thiazole (**2a**). The 6-chloro-3-methyl and 6-chloro-2,3-dihydro derivatives (**2b**, **4**) were prepared from the corresponding carboxymethylimino compounds (**1b**, **3**) using this procedure.



1 2

a, H
b, CH_3

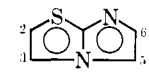


3 4

The susceptibility of this π-excessive system to electrophilic attack permitted the preparation of a variety of 5-substituted 6-chloroimidazo[2,1-*b*]thiazoles (Table II). Nmr data (Table I) were consistent with electrophilic attack at the 5 position. This is in agreement with some chemical studies of Pyl, *et al.*,[4] as well as nmr studies of Pentimalli, *et al.*,[7] on alkyl- and arylimidazo-[2,1-*b*]thiazoles.

A series of Mannich bases (**5–10**) was prepared by treating **2a** with CH_2O and a secondary amine in the presence of AcOH. The acidic nature of the medium was critical, as no reaction occurred in the absence of acid, while in the presence of HCl only a bismethylene compound (**11**) was obtained. Heating one of the aminoalkylated derivatives (the dimethylaminomethyl compound) with HCl also gave **11**. This seems to indicate that the Mannich base is the product of kinetic control and that the bis compound **11** is the product of thermodynamic control, at least in HCl.

TABLE I
NMR DATA IN $CDCl_3$



No.	Substituents	δ values 2-H	3-H	5-H
2a	6-Cl	6.88 ud[a,b]	7.39 ud	7.39 s[c,d]
2b	6-Cl-3-Me	6.45 m[e,f]		7.27 s
18	6-Cl-5-CHO	7.15 ud	8.26 ud	
14	5,6-Cl_2	6.97 ud	7.35 ud	
36	5,6-Me_2	6.69 ud	7.17 ud	

[a] ud = unsymmetrical doublet. [b] The coupling constant of the doublets was 4.5 cps. [c] s = singlet. [d] This band was superimposed onto the doublet representing the 3 position, thus there were three peaks in this region. [e] m = multiplet. [f] This tight multiplet should show up as a quartet at higher resolution. The splitting is due to the 5-Me, which is also split. This mutual splitting of a ring proton on an aromatic system and a methyl group on an adjacent ring carbon is seen in the spectrum of 2,4-dimethylthiazole: N. S. Bhacca, L. F. Johnson, and J. N. Schoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962.

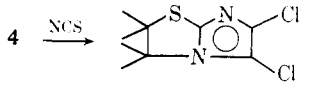
Nitration of **2a** proceeded smoothly and in good yield at 20° to give the 6-chloro-5-nitro derivative (**16**). Reduction of **16** in the presence of Ac_2O gave the expected N-acetyl derivative (**17**). The attempted preparation of a primary amine, as the free base or HCl salt, by hydrogenation of **16** gave only intractable oils.

Potassium thiocyanate and Br_2 in AcOH were used to effect thiocyanation.[8] Hydrolysis of the thiocyanate derivative **12** with H_2SO_4 gave the thiolcarbamate **13**.

The Vilsmeier–Haack reaction was used to give the aldehyde **18**. LAH reduction of **18** gave the methylol **19**. Although this aldehyde (**18**) readily formed some of the carbonyl derivatives such as the semicarbazone **21**, oxime **23**, hydrazone **22**, and nitrovinylene **20**, it failed to condense with diethyl malonate under standard conditions[9] and was rather resistant to oxidation to the carboxylic acid in the presence of H_2O_2, H_2CrO_4, or basic $KMnO_4$ at room temperature. Attempted oxidations at higher temperatures resulted in extensive decomposition. This reluctance toward oxidation and condensation with diethyl malonate may be associated with the presence of the formyl group at a position of such high electron density that the attempted advances of a nucleophile are resisted.

(1) Part I of this series: J. P. Paolini, *J. Org. Chem.*, **33**, 888 (1968).
(2) Presented in part at the 3rd Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1–2, 1968.
(3) For a review see W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p 157.
(4) T. Pyl, R. Giebelmann, and H. Beyer, *Ann.*, **643**, 145 (1961).
(5) I. Iwai and T. Hiroaka, *Chem. Pharm. Bull.* (Tokyo), **12**, 813 (1964), used the bromoacetone as well as its anhydride propargyl bromide.
(6) J. Druey, *Helv. Chim. Acta*, **24**, 226 (1941).
(7) L. Pentimalli, A. Cogo, and A. M. Guerra, *Gazz. Chim. Ital.*, **97**, 488 (1967).
(8) K. Takatori and H. Nishida, *J. Pharm. Soc. Japan*, **71**, 1367 (1951); *Chem. Abstr.*, **46**, 8099 (1952).
(9) C. F. H. Allen and F. W. Spangler in "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p 377.

5,6-Dihalogenated compounds (**14**, **15**) were prepared by treatment of **2a** with N-chloro- or N-bromosuccinimide and the site of attack was determined by means of nmr spectroscopy. The 2,3-dihydro compound (**4**) also formed a dichloro compound (**31**) with N-chlorosuccinimide.



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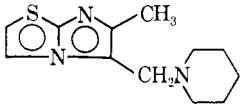
The carboxylic acid **26**, which we were unable to obtain by oxidation of the aldehyde, was prepared in several steps from the aldoxime **23**. This was dehydrated to the nitrile (**24**) with $SOCl_2$. Acid hydrolysis of **24** gave the amide **25** which in turn was converted to the acid **26** by treatment with alkali.

Oximino ethers **27**–**30** were prepared by treating the oxime in methanolic NaOMe with the appropriate organic halide (MeI, allyl chloride, propargyl bromide, and 3,4,5-trimethoxybenzyl chloride).

Piperidinomethyl derivatives of 6-methylimidazo[2,1-*b*]thiazole and 2-chloroimidazo[1,2-*a*]pyridine (**32**, **33**) were prepared in the same manner as the other Mannich bases in this study for pharmacological comparison with 6-chloro-5-piperidinomethylimidazo[2,1-*b*]thiazole (**9**).



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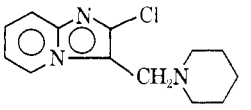

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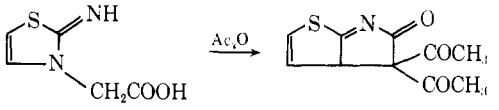
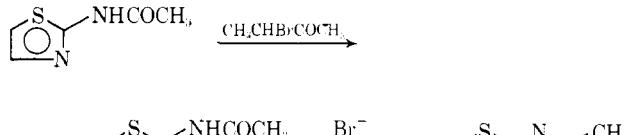
The reaction of the carboxyiminothiazoline (**1a**) and Ac_2O was found to give 5,6-dihydro-5,5-diacetylimidazo[2,1-*b*]thiazol-6-one (**34**).



1a **34**

5,6-Dimethylimidazo[2,1-*b*]thiazole (**36**) was prepared as a standard for the nmr study from 2-acetamidothiazole and 3-bromobutanone according to the procedure used by Iwai[3] for the preparation of 6-methylimidazo[2,1-*b*]thiazole. Heating the intermediate quaternary salt (**35**), which was isolated but not characterized, in dilute HCl gave the 5,6-dimethyl derivative **36**.



35 **36**

Experimental Section

Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. The nmr spectra were run in a Varian A-60A nmr spectrophotometer using TMS as the internal standard. Yields of analytically pure material, melting points, recrystallization solvents, and molecular formulas are shown in Tables II and III.

Analgetic Activity.—The phenylquinone writhing test[10] was used to screen for analgetic activity. Compounds (250 mg/kg) were administered orally to male mice (Charles River, Sprague Dawley CD-1) weighing 18–30 g. Only two of the compounds tested, 6-chloroimidazo[2,1-*b*]thiazole (**2a**) and its dimethylaminomethyl derivative (**5**) inhibited phenylquinone-induced writhing in 50 and 70% of the mice, respectively. Aspirin (250 mg/kg *po*) inhibited writhing in 50% of the mice tested.

Antihypertensive Activity. Blood pressure measurements were made on male renal hypertensive cats[11] (Charles River, Sprague Dawley CD) who had received oral doses (250 mg/kg) of the compounds. Hydralazine (5 mg/kg *po*) normally produces a 30-mm drop in blood pressure in this test. 6-Chloro-5-pyrrolidinomethyl- and 6-chloro-5-piperidinomethylimidazo[2,1-*b*]thiazoles (**8**, **9**) showed blood pressure changes of −31 and −27 mm, respectively. The inactivity of the other aminoalkylated derivatives (**5**, **7**, **10**) indicates some amine specificity. That the chlorine atom appears to be essential to activity is indicated by the inactivity of 6-methyl-5-piperidinomethylimidazo[2,1-*b*]thiazole (**32**). 2-Chloro-3-piperidinomethylimidazo[1,2-*a*]pyridine (**33**), in which the thiazole ring of **6** has been replaced by a pyridine ring, was inactive, indicating some rather rigid requirements for activity with this type of system.

Antimicrobial Activity. The compounds were tested *in vitro* against *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Candida albicans*, and *Trichophyton mentagrophytes*. The 6-chloro-5-nitrovinyl derivative **20** totally inhibited the growth of *C. albicans* at 2.5 μg/ml in the presence of 10% horse serum but was inactive *in vivo*. The 5-nitro-6-chloro derivative **16** as well as the 6-chloro-5-thiocyanato compound **12** and its hydrolysis product, the thiolcarbamate **13**, were active against *T. mentagrophytes* at 100 μg/ml.

Antiinflammatory Activity. The antiinflammatory model used was the carrageenin abscess test.[12] Female rats (Charles River, Sprague Dawley CD) weighing 60–80 g were given the compounds at doses of 250 mg/kg *po*. Phenylbutazone (50 mg/kg *po*) was used for comparison. The compounds producing a decrease of 20% or more in abscess weight are shown in Table IV. 6-Methylimidazo[2,1-*b*]thiazole has been reported to possess antiinflammatory activity;[13] however, 6-chloroimidazo[2,1-*b*]thiazole (**2a**), an isostere of this compound, showed only weak activity. The Mannich bases having cyclic amines (**8**–**10**) showed weak activity. In contrast to the antihypertensive activity, the Cl atom does not appear to be an antiinflammatory activity parameter with these aminoalkylated derivatives, as 6-methyl-5-piperidinomethylimidazo[2,1-*b*]thiazole (**32**) demonstrated the same level of activity. However, the thiazole ring does appear to be essential to antiinflammatory activity, since 2-chloro-3-piperidinomethylimidazo[1,2-*a*]pyridine (**33**) was inactive. Compounds **14**, **15**, **24**, and **25** demonstrated good activity; however, symptomatology was observed with **14** and **15** at 810 mg/kg.

6-Chloroimidazo[2,1-*b*]thiazoles (2a, 2b, 4).—A mixture of the 3-carboxymethyl-2-iminothiazoline (or thiazolidine) (**1a**, **1b**, or **3**, 0.1 mole) and $POCl_3$ (100 ml) was heated under reflux for 2 hr during which time solution occurred. The excess $POCl_3$ was removed by evaporation *in vacuo*, leaving a dark syrupy residue. This syrup was poured, with stirring, into an ice–H_2O mixture and, after solution was complete, aqueous NaOH was added until the mixture was basic. The product separated and could be isolated either by filtration or by extraction with $CHCl_3$. Purification was effected by crystallization of either the free base or the HCl salt.

5,6-Dihaloimidazo[2,1-*b*]thiazoles (14, 15, 31). A mixture containing the 6-chloroimidazo[2,1-*b*]thiazole (**2a**) (0.075 mole) and the appropriate N-halosuccinimide (0.09 mole) in $CHCl_3$ was heated on a steam bath for 5 min and then stirred at room temperature for 20 min. A 20% Na_2CO_3 solution (100 ml) was then added and this mixture was stirred for 10 min. The organic layer was then separated and dried (Na_2SO_4) and the solvent was removed by evaporation. The residue, dissolved in Et_2O, was percolated through a column of acid-washed alumina (30 g) and the column was then washed with Et_2O (200 ml). The solvent

(10) L. C. Hendershot and J. Forsaith, *J. Pharmacol. Exptl. Therap.*, **125**, 237 (1959).

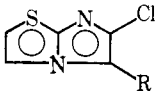
(11) A. Grollman, *Proc. Soc. Exptl. Biol. Med.*, **57**, 102 (1944).

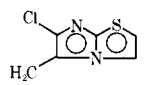
(12) S. Goldstein and M. Schnall, *Arch. Intern. Pharmacodyn.*, **144**, 260 (1963).

(13) Sankyo Co., Ltd., Netherlands Patent 6,502,577 (1965).

TABLE II

5-SUBSTITUTED 6-CHLOROIMIDAZO[2,1-*b*]THIAZOLES



No.	R	Yield, %[a]	Mp, °C	Crystn solvent	Formula[b]
2a	H	87.5	84–86	Hexane	$C_5H_3ClN_2S$[c]
5	$CH_2N(CH_3)_2$	13.9	192–193[d]	*i*-PrOH	$C_8H_{10}ClN_3S \cdot HCl$
6	$CH_2N(C_2H_5)_2$	27.1	181–183[d]	*i*-PrOH	$C_{10}H_{14}ClN_3S \cdot HCl$
7	$CH_2N(C_2H_4OH)_2$	26.7	144–146[d]	MeOH	$C_{10}H_{14}ClN_3O_2S \cdot HCl$
8		70.5	122–124	C_7H_{16}	$C_{10}H_{12}ClN_3S$
9		66.5	110–111	C_7H_{16}	$C_{11}H_{14}ClN_3S$
10		58.3	126–128	PhMe	$C_{10}H_{12}ClN_3OS$
11		73.2	242–244	PhMe	$C_{11}H_6ClN_4S_2$
12	SCN	29.0	197–200	MeOH	$C_6H_2ClN_3S_2$
13	$SCONH_2$	13.0	143–147	EtOH	$C_6H_4ClN_3OS_2$
14	Cl	52.5	112–113	Cyclohexane	$C_5H_2Cl_2N_2S$[e]
15	Br	92.3	133–135	Skellysolve V	$C_5H_2BrClN_2S$
16	NO_2	86.5	192–194	PhMe	$C_5H_2ClN_3O_2S$[f]
17	$NHCOCH_3$	38.8	131–133	C_6H_{14}	$C_7H_6ClN_3OS$
18	CHO	57.0	140–142	EtOH	$C_6H_3ClN_2OS$
19	CH_2OH	46.6	225–235 dec	PhMe	$C_6H_4ClN_2OS$
20	$CH{=}CHNO_2$	29.0	197–200	MeOH	$C_7H_4ClN_3O_2S$
21	$CH{=}NNHCONH_2$	18.5	>250 dec	DMF	$C_7H_6ClN_5OS$
22	$CH{=}NNH_2$	10.5	125–126	C_6H_6	$C_6H_5ClN_4S$
23	CH=NOH	23.9	202–203	PhMe	$C_6H_4ClN_3OS$
24	CN	90.0	174–176	C_6H_6	$C_6H_2ClN_3S$
25	$CONH_2$	49.6	166–168	*i*-PrOH	$C_6H_4ClN_3OS$
26	COOH	40.6	205 dec	DMF–H_2O	$C_6H_3ClN_2O_2S$
27	$CH{=}NOCH_3$	4.0	130–134	EtOH–H_2O	$C_7H_6ClN_3OS$
28	$CH{=}NOCH_2CH{=}CH_2$	16.9	170–177	*i*-PrOH	$C_9H_8ClN_3OS$
29	$CH{=}NOCH_2C{\equiv}CH$	14.4	137–138	*i*-PrOH	$C_9H_6ClN_3OS$
30	$CH{=}NOCH_2$-3,4,5-$(OCH_3)_3C_6H_2$	14.7	139–140	EtOH	$C_{16}H_{16}ClN_3O_4S$

[a] These are the yields of analytically pure material. [b] All compounds were analyzed for C, H, N and are within ±0.4% unless otherwise indicated. [c] Cl: calcd, 22.36; found, 22.44. [d] HCl salt. [e] C: calcd, 31.11; found, 31.53. [f] C: calcd, 29.49; found 30.10. Cl: calcd, 17.41; found, 17.39.

TABLE III

MISCELLANEOUS COMPOUNDS

No.	Yield, %[a]	Mp, °C	Recrystn solvent	Formula[b]
2b	9.5	101–103	C_6H_{14}	$C_6H_5ClN_2S$
3	50.6	234–240	H_2O	$C_5H_8N_2O_2S$
4	52.2	183–186[c]	*i*-PrOH–C_6H_{14}	$C_5H_5ClN_2S \cdot HCl$
31	89.0	86–89	C_6H_{14}	$C_5H_4Cl_2N_2S$
32	29.4	88–90	C_6H_{14}	$C_{12}H_{17}N_3S$
33	63.4	126–128	C_6H_{14}	$C_{13}H_{16}ClN_3$
34	61.6	230–235	PhMe	$C_9H_8N_2O_3S$
36	4.2	89–91	C_6H_{14}	$C_7H_8N_2S$

[a] These are the yields of analytically pure material. [b] See Table II, footnote *b*. [c] HCl salt.

TABLE IV

ANTIINFLAMMATORY ACTIVITY

No.	Level of act.[a]	No.	Level of act.[a]
2a	A	19	A
4	A	22	A
8	A	24	C
9	A	25	C
10	A	27	A
14	B	32	A
15	B	Phenylbutazone	B

[a] Decrease in abscess weight: A = 20–30% (weak), B = 30–40%, C = 40–50%.

was removed from the effluent liquid and the residue was purified by crystallization.

5-Acetamido-6-chloroimidazo[2,1-*b*]thiazole (17).—A mixture of 6-chloro-5-nitroimidazo[2,1-*b*]thiazole (**16**) (13.6 g, 0.067 mole), Ac_2O (25 ml), and 10% Pd–C (1.5 g) in AcOH (100 ml) was shaken under 3.1 kg of H_2/cm² until the theoretical amount of H_2 was absorbed. The mixture was filtered through a Celite pad. The solvent was removed from the filtrate, by evaporation *in vacuo*, with heat. The residual oil was poured onto ice and the resulting solid was filtered off and washed with cold H_2O and purified.

6-Chloroimidazo[2,1-*b*]thiazole-5-thiolcarbamate (13).—To concentrated H_2SO_4 (100 ml), maintained at 10°, was added 6-chloro-5-thiocyanatoimidazo[2,1-*b*]thiazole (**12**) (28 g, 0.13 mole). After the addition was complete, the reaction mixture was stirred for an additional 1 hr, then poured onto ice, the resulting solid was filtered off, washed with H_2O, and purified.

6-Chloroimidazo[2,1-*b*]thiazole-5-carboxaldehyde (18).—$POCl_3$ (15.5 g, 0.1 mole) was added to a cooled mixture of DMF (7.5 g, 0.1 mole) in $CHCl_3$ (150 ml). Then 6-chloroimidazo[2,1-*b*]thiazole (**2a**) (15.9 g, 0.1 mole) was added cautiously to the DMF–$POCl_3$ complex. After addition was complete, the reaction mixture was heated under reflux for 2 hr. The solvent was removed by evaporation *in vacuo* and the residue was poured into ice and H_2O. The resulting solid was filtered off, washed well with H_2O, and purified.

6-Chloroimidazo[2,1-*b*]thiazole-5-aldoxime (23).—$NH_2OH \cdot HCl$ (3.5 g, 0.05 mole) in H_2O (25 ml) was added to a boiling solution of 6-chloroimidazo[2,1-*b*]thiazole-5-carboxaldehyde (**18**) (9.3 g, 0.05 mole) in EtOH (150 ml). The reaction mixture was boiled for 15 min, then cooled, and the solid was filtered off and purified.

Oximino Ethers (27–30).—Na (2.3 g, 0.1 g-atom) was added to MeOH (200 ml) and, after all of the Na had been consumed, 6-chloroimidazo[2,1-*b*]thiazole-5-aldoxime (**23**) (20.2 g, 0.1 mole) was added. After 15 min, the alkyl halide (0.1 mole) was added to the reaction mixture and heated under reflux for 2 hr. The solvent was removed by evaporation *in vacuo* and the residue was triturated with hot *i*-PrOH and filtered. The filtrate was diluted with H_2O and the resulting solid was filtered off, dried, and purified by crystallization.

6-Chloro-5-thiocyanatoimidazo[2,1-*b*]thiazole (12) was prepared from 6-chloroimidazo[2,1-*b*]thiazole (**2a**) (15.8 g, 0.1 mole), KSCN (15.5 g, 0.16 mole), Br_2 (16 g, 0.1 mole), and AcOH according to the procedure of Takatori and Nishida.[8]

6-Chloro-5-(2-nitrovinyl)imidazo[2,1-*b*]thiazole (20) was prepared from 6-chloroimidazo[2,1-*b*]thiazole-5-carboxaldehyde (**18**) (37 g, 0.20 mole) and $MeNO_2$ (12 g, 0.2 mole) according to the procedure of Worrall,[14] utilizing a mixture of MeOH (200 ml) and THF (200 ml) as the solvent.

6-Chloroimidazo[2,1-*b*]thiazole-5-carboxaldehyde Hydrazone (22).—Aldehyde **18** (18.7 g, 0.1 mole) was added to a refluxing solution of 95% NH_2NH_2 (16 g, 0.95 mole) in EtOH (300 ml). The mixture was heated for 3 hr then cooled until a solid separated. This solid was filtered off and dried.

6-Chloroimidazo[2,1-*b*]thiazole-5-carboxaldehyde Semicarbazone (21).—Semicarbazide hydrochloride (5.5 g, 0.05 mole) and NaOAc (8.2 g, 0.1 mole) were added to a solution of **18** (9.3 g, 0.05 mole) in boiling 50% aqueous EtOH (200 ml). A solid formed and was filtered off and washed (EtOH).

6-Chloro-5-cyanoimidazo[2,1-*b*]thiazole (24).—6-Chloroimidazo[2,1-*b*]thiazole-5-aldoxime (**23**) (10 g, 0.05 mole) was added in small portions to $SOCl_2$ (60 ml). The reaction was exothermic and after the addition of the aldoxime had been completed the reaction mixture was heated under reflux until complete solution was effected. The solvent was then removed by evaporation *in vacuo*. The residue was poured onto ice and the resulting solid was filtered off, washed (H_2O), and dried.

5-Carbamoyl-6-chloroimidazo[2,1-*b*]thiazole (25).—6-Chloro-5-cyanoimidazo[2,1-*b*]thiazole (**24**) (25.7 g, 0.14 mole) was added with stirring, in small portions, to cold (10°) concentrated H_2SO_4 (100 ml). After the addition was complete, the reaction mixture was refrigerated for 16 hr then poured onto ice; the resulting white solid was filtered off, washed (H_2O), and dried.

6-Chloroimidazo[2,1-*b*]thiazole-5-carboxylic Acid (26).—A mixture containing 5-carbamoyl-6-chloroimidazo[2,1-*b*]thiazole (**25**) (10 g, 0.05 mole) and NaOH (5 g, 0.12 mole) in 250 ml of H_2O–MeOH (4:1) was heated under reflux for 2 hr. The solvent was removed by evaporation *in vacuo* and the residue was taken up in $CHCl_3$ and washed with H_2O. The aqueous layer was acidified (AcOH) and the resulting solid was filtered off and washed (H_2O).

6-Chloro-5-hydroxymethylimidazo[2,1-*b*]thiazole (19).—Aldehyde **18** (9.3 g, 0.05 mole) was added to LAH (2.0 g, 0.06 mole) in THF. The mixture was heated under reflux with stirring for 15 min and then cooled in an ice bath. HCl (40 ml of 10% solution) was then added dropwise with stirring. The mixture was then filtered. The solvent was removed from the filtrate by evaporation *in vacuo* and a solid was obtained.

5,6-Dimethylimidazo[2,1-*b*]thiazole (36) was prepared from 2-aceramilothiazole (75 g, 0.53 mole) and 3-bromobutanone (79 g, 0.53 mole), according to the procedure used by Iwai[8] for the preparation of 6-methylimidazo[2,1-*b*]thiazole.

3-Carboxymethyl-2-iminothiazolidine (3) was prepared from sodium chloroacetate (20 g, 0.17 mole) and 2-aminothiazoline (10.2 g, 0.1 mole) according to the procedure used by Erney[9] for the preparation of 2-carboxymethyl-2-iminothiazoline.

Bis(6-chloroimidazo[2,1-*b*]thiazolyl)methane (11). A mixture containing 6-chloroimidazo[2,1-*b*]thiazole (**2a**) (17.0 g, 0.05 mole), 37% CH_2O solution (8.1 g, 0.1 mole), and concentrated HCl (15 ml) in H_2O (100 ml) was heated on a steam bath for 15 min. The mixture was then cooled and the resulting solid was filtered off and purified.

5,5-Diacetylimidazo[2,1-*b*]thiazol-6(5*H*)-one (34). A mixture containing 2-carboxymethyl-2-iminothiazoline (**1a**) (20 g, 0.125 mole) and Ac_2O (50 ml) in C_6H_6 was heated under reflux with stirring for 29 hr. The C_6H_6 was removed by evaporation *in vacuo*. The residue was poured into ice–H_2O and the resulting solid was filtered off, washed with H_2O, dried, and purified.

6-Chloro-5-nitroimidazo[2,1-*b*]thiazole (16). Concentrated HNO_3 (50 ml) was added dropwise to a solution of the 6-chloroimidazo[2,1-*b*]thiazole (**2a**) (47.6 g, 0.3 mole) in concentrated H_2SO_4 (350 ml). The temperature of the reaction mixture was maintained between 5 and 10° during addition of the HNO_3. After addition of the HNO_3 was complete, the reaction mixture was poured onto ice with stirring. The resulting solid was filtered off, washed well (H_2O), and purified.

Caution: This compound was irritating to the skin and produced sneezing.

Preparation of the Mannich Bases (5–10, 32, 33). A mixture containing the imidazothiazole or the imidazopyridine (0.1 mole), formalin (8.1 g, 0.1 mole of CH_2O), and AcOH (20 ml) in MeOH (125 ml) was heated under reflux for 6 hr. The solvent was removed by evaporation *in vacuo* and the residue was triturated with H_2O and made basic with NaOH. The resulting mixture was extracted with $CHCl_3$ (200 ml) and this organic layer was then separated and dried (Na_2SO_4). The solvent was then removed by evaporation *in vacuo* and the residue was purified by crystallization of either the free base or the HCl salt.

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(14) D. E. Worrall in "Organic Syntheses," Coll. Vol. I, H. Gilman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1932, p 413.