Cyclization of Isothiosemicarbazones. I. A New Route to 2-Mercaptoimidazole Derivatives and 4-Substituted Imidazoles[1)]

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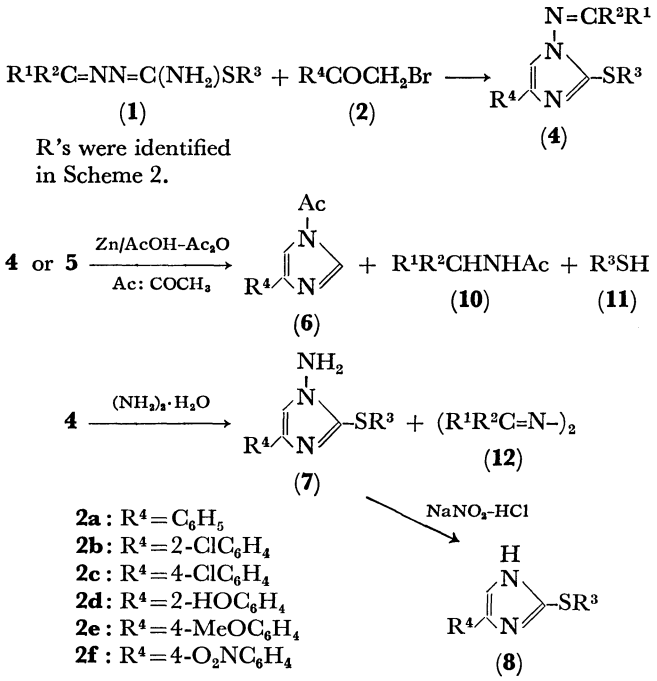
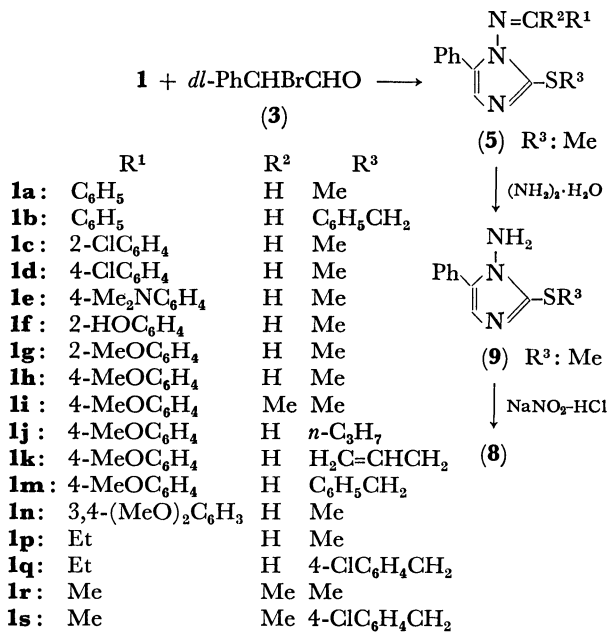
Some 1-arylmethyleneamino-2-mercapto-4-aryl-1*H*-imidazole derivatives were prepared by the condensation of isothiosemicarbazones of aromatic carbonyl compounds with phenacyl bromides. The 1,2,5-trisubstituted isomers were obtained by substitution of *dl*-α-bromophenylacetaldehyde for phenacyl bromide in this condensation. The reaction of isothiosemicarbazones of aliphatic carbonyl compounds with phenacyl bromides produced a dark, complex mixture from which the corresponding 1-alkylideneamino-2-mercapto-4-aryl-1*H*-imidazoles and 3,5-disubstituted 1,2,4-triazines were isolated in poor yields, with the latter being a main product or a sole heterocyclic product depending on the reaction conditions. Reductive cleavage of the cyclized products with zinc dust in acetic acid-acetic anhydride solution gave 1-acetyl-4-aryl-1*H*-imidazoles, which were readily hydrolyzed to 4-aryl-1*H*-imidazoles. The susceptibility to acid hydrolysis of the arylmethyleneamino group was dependent on the extent of conjugation between the azomethine double bond and the adjacent aromatic rings. Hydrazinolysis of the azomethine double bond yielded 1-amino-2-mercapto-4-aryl-1*H*-imidazoles in high yields. Their structures were established on the basis of NMR, IR, UV, and mass spectra as well as elemental analyses. Differentiation between 1,2,4- and 1,2,5-trisubstituted imidazoles was discussed.

Condensation of certain thiosemicarbazones of aromatic aldehyde with α-halo ketones leads to the formation of thiazole derivatives owing to the preferential attack of the most nucleophilic mercapto group on the halogen-bearing carbon of the halo ketone.[2)] If the potential mercapto group, however, is first blocked by alkylation, the reaction of *S*-alkylisothiosemicarbazone with an α-halo ketone should lead to the formation of an alkylthioimidazole. Very few examples have been known for cyclization of isothiosemicarbazone to a heterocyclic compound with retention of the alkylthio group.[3)] The present paper is concerned with an attempt to prepare imidazole derivatives by blocking the mercapto group of thiosemicarbazone with an alkyl, alkenyl, or arylalkyl group and condensing the isothiosemicarbazones with α-halo carbonyl compounds. The use of isothiosemicarbazone, especially of aromatic carbonyl compounds, allows to avoid extensive sulfide formation as encountered with the reaction between phenacyl bromide and *S*-benzylisothiourea[4)] which has a pronounced tendency to lose the thiol. This paper further describes reductive and hydrolytic cleavage of as well as hydrazinolysis of the cyclized products, as represented in Schemes 1 and 2.

In view of the fact that the condensation of isothiosemicarbazones (**1**) with *dl*-α-bromophenylacetaldehyde (**3**) gave sterically hindered 5-phenyl compounds (**5**), steric factor, as suggested in our preliminary report,[1)] should not be the directive force in the orientation of this ring closure. Differentiation between 4- and 5-phenyl-1*H*-imidazoles was made by observing the ortho deshielding phenomenon[5)] of the 4-phenyl protons and the C–H stretching absorption band at 5-position of the 1,2,4-trisubstituted imidazole series. Mass spectra showed no definitive difference between both isomers in



Scheme 1.



	R^1	R^2	R^3
1a:	C_6H_5	H	Me
1b:	C_6H_5	H	$C_6H_5CH_2$
1c:	2-ClC_6H_4	H	Me
1d:	4-ClC_6H_4	H	Me
1e:	4-$Me_2NC_6H_4$	H	Me
1f:	2-HOC_6H_4	H	Me
1g:	2-$MeOC_6H_4$	H	Me
1h:	4-$MeOC_6H_4$	H	Me
1i:	4-$MeOC_6H_4$	Me	Me
1j:	4-$MeOC_6H_4$	H	*n*-C_3H_7
1k:	4-$MeOC_6H_4$	H	H_2C=$CHCH_2$
1m:	4-$MeOC_6H_4$	H	$C_6H_5CH_2$
1n:	3,4-$(MeO)_2C_6H_3$	H	Me
1p:	Et	H	Me
1q:	Et	H	4-$ClC_6H_4CH_2$
1r:	Me	Me	Me
1s:	Me	Me	4-$ClC_6H_4CH_2$

Scheme 2.

determining the substitution pattern with the exception of compounds carrying an ortho-substituent on the arylmethyleneamino group.

Results and Discussion

The condensation of isothiosemicarbazones (**1**) with phenacyl bromides (**2**) was carried out by heating a mixture of **1** and **2** in acetonitrile in the presence of an excess of sodium hydrogencarbonate at 75 °C for 3 h under stirring. With a few exceptions, the imidazoles usually crystallized out of the reaction mixture upon cooling or even at still hot and could easily be isolated by filtration. Most of the products, after being washed with water to remove any inorganic salts, were sufficiently pure to use for further reactions indicated in Scheme 1. Isolation of **4h**, **4m**, and **4p** was accomplished by means of column chromatography. 2-Allylthio compound **4t** was isolated by crystallization from ethanol of an amorphous gum obtained after evaporation of the reaction mixture under reduced pressure. Alternative process in which a mixture of **1** and **2** (2: 1) in ethanol is heated at 75 °C (Method A) could be applied to the cyclization of **1e** to **4h** with rather better yields than in the standard procedure described above. In some cases, the use of excess **2** up to 50% was found to somewhat improve the yield of imidazoles. For example, the yield of **4j** increased to 66% when the ratio of **2a** to **1g** was raised to 1.5: 1 compared with the yield 40% in the ratio 1: 1. This modification, however, was not generally applicable because the excess **2** may prevent crystallization of a cyclized product from the reaction mixture. The use of a tertiary amine such as pyridine or triethylamine in place of sodium hydrogencarbonate resulted in the predominant formation of the corresponding quaternary ammonium bromide of these acid binders with **2** and gave no cyclized product. Attempts to cyclize **1s** and *p*-methoxyacetophenone *S*-benzylisothiosemicarbazone with **2a** were unsuccessful presumably due to their sterically unfavorable structure. Cyclization of *m*- and *p*-nitrobenzaldehyde *S*-methylisothiosemicarbazones was also failed because of the extremely poor solubility.

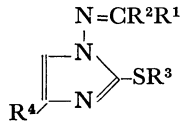
In sharp contrast to the behavior of the isothiosemicarbazones of aromatic carbonyl compounds, the reaction of those of aliphatic ones with **2** produced a dark resinous mass even at room temperature with a poor yield of imidazoles and therefore might be less valuable for preparative purpose. Isolation of the 1-alkylideneamino-1*H*-imidazoles (**4w**—**4z**) was accomplished by means of column chromatography on silica gel using a benzene–ethanol mixture as an eluent. Unfortunately, **4z** tends to lose the acetone during the working up to form **7a** and therefore the conversion of **1r** to imidazole was estimated on the basis of the yield of a relatively insoluble derivative such as **4o** which was obtained by reacting both **4z** and **7a** with anisaldehyde in an acidic medium. 4-Aryl-1*H*-imidazoles thus obtained were listed in Table 1.

The reaction of aliphatic isothiosemicarbazones with **2** was further complicated by the formation of 3,5-disubstituted 1,2,4-triazines (**15**) and sulfides (R^3SCH_2-COR^4) in addition to **4**, with the ratio of these products being dependent upon the particular isothiosemicarbazone and the reaction conditions. The standard procedure described in the beginning of this section generally gives **4** as a main product along with a minor product **15**, while the latter predominates under the conditions of Method A. For example, the reaction of **1p** with **2a** by that method produced 3-methylthio-5-phenyl-1,2,4-triazine (**15a**) in 8% yield with no imidazole formation, whereas the reaction of **1q** with **2a** in dimethyl sulfoxide (DMSO) in the presence of sodium hydrogencarbonate gave **4y** in 11% yield but no **15c** at all. Under the conditions of Method A, **15b** was obtained in less than 30% yields from the reaction of **1p** or **1r** with **2c**. Similarly, **1s** gave **15c** in 38% yield. The structure of **15a** was confirmed by the unambiguous synthesis reported by Paudler *et al.*[6] and **15b** was well consistent in the melting point with that of the literature.[7]

The triazine formation was attributed to the tendency of an aliphatic isothiosemicarbazone to split off the carbonyl component and can be explained as the result of oxidation at the α-carbon of **2** by isothiosemicarbazide (**13**) thus liberated by analogy with osazone or dioxime formation of α-halo carbonyl compounds.[8] Since the reaction mixture becomes acidic under the conditions of Method A, the rate of hydrolysis of isothiosemicarbazone should increase and the triazine formation will be accelerated. On the other hand, acidic media are generally unfavorable to the imidazole formation because protonation of **1** evidently inhibits the first step of this cyclization (Fig. 2). Furthermore, aldehyde isothiosemicarbazones, particularly those of aliphatic aldehyde, are likely susceptible to intramolecular cyclization under such conditions through the addition of the terminal amino group to the aldimine double bond to form a dihydro-1,2,4-triazole structure which is believed to be an intermediate in the formation of *N*-isopropenyl-1,2,4-triazoles in acetic acid.[9] Thus **1p** or **1q** cannot produce the corresponding 1-propylideneamino-1*H*-imidazole by the reaction with **2** or **3** unless a stronger base than the isothiosemicarbazone itself is present as acid binder. The fact that **1q** does not give **15c** in DMSO in the presence of sodium hydrogencarbonate can be rationalized in terms of the strong proton-accepting nature of this solvent. The reaction of **13** ($R^3=CH_3$) with **2** produced a highly darkened, complex mixture from which the corresponding **15** was isolated only in 4—8% yields. The alkylidene group of aliphatic isothiosemicarbazone may therefore serve as a protective group for controlled liberation of relatively unstable **13**, thereby leading to better yields of **15**. Taking into account of the facts that ammonium bromide and **14** ($R^3=CH_3$) were isolated in significant amounts from the reaction mixture of **1r** with **2a** and that the triazine formation occurred in the absence of oxygen, a mechanism for this reaction was suggested in Fig. 1.

The reaction conditions employed for the preparation of **4** were not very suitable for the reaction of **1** ($R^1=$ aryl) with **3** because of unstability of the halo aldehyde to sodium hydrogencarbonate. With the exception of **1p**, the condensation of **1** with **3** was thus carried out by

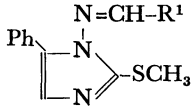
TABLE 1. 1-ALKYLIDENEAMINO- AND 1-ARYLMETHYLENEAMINO-2-MERCAPTO-4-ARYL-1*H*-IMIDAZOLES



Compd No.	R^1	R^2	R^3	R^4	Yield (%)	Mp °C	Formula	Found (Calcd), % C	H	N	M^+	IR[a] νC–H
4a	C_6H_5	H	Me	C_6H_5	70	144—145[b]	$C_{17}H_{15}N_3S$	69.33 (69.60	5.09 5.15	14.21 14.32	293 293)	3140
4b	C_6H_5	H	Me	*p*-ClC_6H_4	78	177—178[c]	$C_{17}H_{14}ClN_3S$	62.00 (62.29	4.34 4.30	12.50 12.82	327 327)	3140
4c	C_6H_5	H	Me	*p*-$MeOC_6H_4$	50	145—145.5[d]	$C_{18}H_{17}N_3OS$	66.80 (66.84	5.22 5.30	12.74 13.00	323 323)	3150
4d	C_6H_5	H	Me	*p*-$O_2NC_6H_4$	80	225—226[e]	$C_{17}H_{14}N_4O_2S$	60.18 (60.34	4.25 4.17	16.36 16.56	338 338)	3150
4e	C_6H_5	H	$C_6H_5CH_2$	C_6H_5	63	128—129[f]	$C_{23}H_{19}N_3S$	74.80 (74.78	5.16 5.18	11.18 11.38	369 369)	3150
4f	*o*-ClC_6H_4	H	Me	C_6H_5	77	149—150[c]	$C_{17}H_{14}ClN_3S$	62.23 (62.29	4.33 4.30	12.68 12.82	327 327)	3150
4g	*p*-ClC_6H_4	H	Me	C_6H_5	78	173.5—174[b]	$C_{17}H_{14}ClN_3S$	62.59 (62.29	4.37 4.30	12.70 12.82	327 327)	3150[j]
4h	*p*-$Me_2NC_6H_4$	H	Me	C_6H_5	49[g]	137—138[h]	$C_{19}H_{20}N_4S$	67.73 (67.84	6.01 5.99	16.82 16.66	336 336)	3150
4i	*o*-HOC_6H_4	H	Me	C_6H_5	73	176—178[b]	$C_{17}H_{15}N_3OS$	65.88 (66.01	4.92 4.89	13.59 13.58	309 309)	3145
4j	*o*-$MeOC_6H_4$	H	Me	C_6H_5	66	146—146.5[i]	$C_{18}H_{17}N_3OS$	67.05 (66.84	5.26 5.30	13.00 13.00	323 323)	3160[k]
4k	*p*-$MeOC_6H_4$	H	Me	C_6H_5	75	169—169.5[m]	$C_{18}H_{17}N_3OS$	66.82 (66.84	5.27 5.30	13.03 13.00	323 323)	3150[j]
4m	*p*-$MeOC_6H_4$	Me	Me	C_6H_5	38[g]	137—138[m]	$C_{19}H_{19}N_3OS$	67.68 (67.64	5.77 5.68	12.15 12.46	337 337)	3140
4n	*p*-$MeOC_6H_4$	H	Me	*o*-ClC_6H_4	58	142—142.5[n]	$C_{18}H_{16}ClN_3OS$	60.89 (60.41	4.39 4.51	11.74 11.74	357 357)	3160
4o	*p*-$MeOC_6H_4$	H	Me	*p*-ClC_6H_4	73	179—179.5[m]	$C_{18}H_{16}ClN_3OS$	60.48 (60.41	4.61 4.51	11.99 11.74	357 357)	3140
4p	*p*-$MeOC_6H_4$	H	Me	*o*-HOC_6H_4	8[g]	149—150[m]	$C_{18}H_{17}N_3O_2S$	64.16 (63.71	5.03 5.05	12.40 12.38	339 339)	3150
4q	*p*-$MeOC_6H_4$	H	Me	*p*-$MeOC_6H_4$	71	156.5—157[p]	$C_{19}H_{19}N_3O_2S$	64.37 (64.48	5.41 5.41	11.67 11.87	353 353)	3140
4r	*p*-$MeOC_6H_4$	H	Me	*p*-$O_2NC_6H_4$	77	215—216[q]	$C_{18}H_{16}N_4O_3S$	58.48 (58.69	4.39 4.38	14.99 15.21	368 368)	3140
4s	*p*-$MeOC_6H_4$	H	*n*-Pr	C_6H_5	67	143—143.5[b]	$C_{20}H_{21}N_3OS$	68.32 (68.36	6.13 6.02	11.73 11.96	351 351)	3120[v]
4t	*p*-$MeOC_6H_4$	H	$H_2C=CHCH_2$	C_6H_5	49	110—111[r]	$C_{20}H_{19}N_3OS$	68.75 (68.75	5.42 5.48	11.82 12.03	349 349)	3140
4u	*p*-$MeOC_6H_4$	H	$C_6H_5CH_2$	C_6H_5	38	136—137[d]	$C_{24}H_{21}N_3OS$	72.20 (72.16	5.32 5.30	10.33 10.52	399 399)	3150
4v	*p*-$MeOC_6H_4$	H	$C_6H_5CH_2$	*p*-ClC_6H_4	47	174—175[s]	$C_{24}H_{20}ClN_3OS$	66.52 (66.43	4.58 4.65	9.66 9.69	433 433)	3140
4w	Et	H	Me	C_6H_5	27[g]	179.5—180[i,u]	$C_{13}H_{16}ClN_3O_4S$	45.05 (45.15	4.60 4.66	12.09 12.15)		3150[t]
4x	Et	H	Me	*p*-ClC_6H_4	22[g]	104—104.5[r]	$C_{13}H_{14}ClN_3S$	55.90 (55.81	5.00 5.04	14.85 15.02)		3140
4y	Et	H	*p*-$ClC_6H_4CH_2$	C_6H_5	28[g]	107.5—108[i]	$C_{19}H_{18}ClN_3S$	63.77 (64.13	5.15 5.10	11.67 11.81)		3150
4z	Me	Me	Me	C_6H_5	8[g]	180—180.5[n,u]	$C_{13}H_{16}ClN_3O_4S$	45.23 (45.15	4.63 4.66	12.29 12.15)		3150[t]

a) The C–H stretching vibration of imidazole ring, cm^{-1} in KBr. b) Pale yellow needles from EtOH. c) Yellow needles from EtOH. d) Yellow plates from benzene–EtOH. e) Bright orange needles from pyridine. f) Light brown needles from MeCN. g) A homogeneous fraction from column chromatography. h) Pale yellow needles from MeOH. i) Yellow prisms from EtOH. j) 3155 cm^{-1} in $CHCl_3$. k) 3155 cm^{-1} in CCl_4. m) Pale yellow needles from benzene–EtOH. n) Colorless needles from EtOH. p) Pale yellow needles from pyridine–*i*-PrOH. q) Brown needles from pyridine. r) Pale yellow plates from EtOH. s) Yellow fine prisms from pyridine–EtOH. t) Free base in CCl_4. u) $HClO_4$ salt. v) Splitted into 3120 and 3090 cm^{-1} bands.

Table 2. 1-Alkylideneamino- and 1-arylmethyleneamino-2-methylthio-5-phenyl-1*H*-imidazoles



Compd No.	R^1	Yield[a] (%)	Mp °C	Formula	Found (Calcd), % C	H	N	M+	UV (MeOH) λ_{max} nm ($\varepsilon\times10^{-4}$)		NMR[e] SCH_3	H-4
5a	C_6H_5	53	110—111[b]	$C_{17}H_{15}N_3S$	69.50 (69.60	5.21 5.15	14.48 14.32	293 293)	263 (2.82)	—	2.66	7.20
5b	*o*-ClC_6H_4	62	109—109.5[b]	$C_{17}H_{14}ClN_3S$	62.01 (62.29	4.37 4.30	12.76 12.82	327 327)	264 (2.28)	—	2.69	7.22
5c	*p*-ClC_6H_4	49	96.5—97[b]	$C_{17}H_{14}ClN_3S$	61.98 (62.29	4.22 4.30	12.88 12.82	327 327)	269 (2.65)	—	2.67	7.22
5d	*o*-HOC_6H_4	71	112—113[b]	$C_{17}H_{15}N_3OS$	65.79 (66.01	4.91 4.89	13.52 13.58	309 309)	267 (2.01)	335 (0.7)	2.68	7.21
5e	*o*-$MeOC_6H_4$	55	59.5—61[c]	$C_{18}H_{17}N_3OS$	66.59 (66.84	5.16 5.30	13.02 13.00	323 323)	267 (2.61)	332 (1.35)	2.67	7.29
5f	*p*-$MeOC_6H_4$	46	95—95.5[b]	$C_{18}H_{17}N_3OS$	67.00 (66.84	5.36 5.30	12.99 13.00	323 323)	281 (2.74)	306 (2.37)	2.67	7.24
5g	Et	15	38—39.5[d]	$C_{13}H_{15}N_3S$	63.80 (63.66	6.14 6.16	17.39 17.13)		276 (1.40)	—	2.61	7.06

a) For the product from a homogeneous fraction of column chromatogram. b) Yellow needles from *i*-PrOH. c) Yellow prisms from hexane–*i*-Pr_2O. d) Pale yellow crystals. e) δ, in $CDCl_3$.

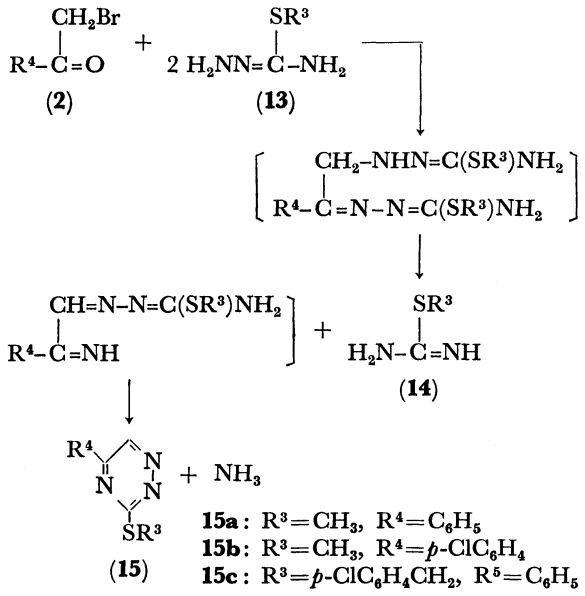
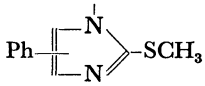


Fig. 1. A reaction mechanism for 1,2,4-triazine formation.

refluxing a mixture of **1** and **3** in a molar ratio of 2: 1 in acetonitrile without added sodium hydrogencarbonate and 5-phenyl-1*H*-imidazoles were isolated by means of column chromatography. As described above, **1p** did not produce the corresponding **5** under these reaction conditions but a complex mixture composed of many unidentifiable components. The standard procedure using sodium hydrogencarbonate was inevitably applied to the preparation of **5g** from **1p** in spite of the poor yield of this imidazole. 5-Phenyl-1*H*-imidazoles (**5**) thus obtained were listed in Table 2.

The structures of **4** and **5** were confirmed on the basis of analytical and spectral data (Tables 1—4) as well as their chemical transformation.

Table 3. Chemical shifts of phenyl protons on the imidazole ring (δ, in $CDCl_3$).



R^1	4-Phenyl H^o	$H^{m,p}$	Δ[a]	5-Phenyl $H^{o,m,p}$
C_6H_5	7.88	7.41	0.47	7.44
o-ClC_6H_4	7.92	7.39	0.53	7.42
p-ClC_6H_4	7.86	7.41	0.45	7.43
o-HOC_6H_4	7.87	7.38	0.49	7.41
o-$MeOC_6H_4$	7.92	7.42	0.50	7.42
p-$MeOC_6H_4$	7.88	7.39	0.49	7.40
Et	7.82	7.37	0.45	7.28

a) Differences (in ppm) between the chemical shifts of *ortho* (H^o) and *meta-para* ($H^{m,p}$) protons.

As has been observed by a number of investigators, the anisotropic deshielding of phenyl protons ortho to the heteroaromatic ring in phenylazoles disappeares or greatly diminishes when coplanarity between the two aromatic rings and the resulting resonance interaction is inhibited by the adjacent alkyl group on the azole ring.[5] The NMR spectral data (Table 3) showed that the ortho protons (H^o) in the compounds **4** obtained from the condensation with **2a** were deshielded by 0.45—0.53 ppm relative to the *meta*- and *para*-protons ($H^{m,p}$), whereas the phenyl protons in the compounds **5** gave a single signal only. Thus the phenyl group of **4** should lie at the position 4 and that of **5** is in the 5-position adjacent to the $R^1R^2C{=}N$ grouping.

Compounds which were derived from substituted phenacyl bromides (**2b**—**2f**) might also be expected to have the 4-aryl-1*H*-structure. The UV spectra of these compounds normally showed two maxima at near

TABLE 4. UV SPECTRA OF 1-ARYLMETHYLENEAMINO-2-METHYLTHIO-4-ARYL-1*H*-IMIDAZOLES

Compd No.	R^4	UV (MeOH) λ_{max} nm ($\varepsilon \times 10^{-4}$)		
4a	C_6H_5	279 (3.09)		344 (1.18)
4b	*p*-ClC_6H_4	283 (3.54)		345 (1.44)
4c	*p*-$MeOC_6H_4$	294 (3.66)		352 (1.27)
4f	C_6H_5	281 (3.37)		356 (1.04)
4g	C_6H_5	283 (3.72)		349 (1.33)
4i	C_6H_5	281 (3.17)		351 (1.84)
4j	C_6H_5	278 (2.74)		349 (1.73)
4k	C_6H_5	291 (2.90)		342 (2.20)
4m	C_6H_5	283 (3.41)		—
4n	*o*-ClC_6H_4	293 (2.46)		338 (2.20)
4o	*p*-ClC_6H_4	292 (3.06)		344 (2.29)
4p	*o*-HOC_6H_4	258 (1.55),	300 (2.70),	352 (2.18)
4q	*p*-$MeOC_6H_4$	290 (2.77)		348 (1.92)

280—290 and 340—350 nm with one or two inflections between these bands, with the former absorptions being more intense than the latter (Table 4). These characteristics in UV spectra are quite similar to those exhibited by 4-(unsubstituted phenyl) compounds (**4a**, **4f—g**, **4i—k**) and are essentially different from those of **5**, which had a main band within the limits λ_{max} 263—281 nm and $\varepsilon \times 10^{-4}$=2.01—2.82. The compound **4p**, which had an additional shorter band at 258 nm and a longer main band at 300 nm than the normal region, exhibited an intramolecularly hydrogen bonded O–H band (centered at 3050 cm^{-1}) at a concentration of 2.5×10^{-3} M in carbon tetrachloride. Such hydrogen bonding would be possible only in the 4-*o*-hydroxyphenyl structure because of lack of proton-accepting nature in N-1. Consequently the reaction between isothiosemicarbazones and phenacyl bromides should produce 4-aryl-1*H*-imidazoles independently of the nature of R's and the steric repulsion between R^4 and R^1R^2C=N groups in the transition state will have no effect upon the orientation of ring closure.

The 1,2,4- and 1,2,5-trisubstituted imidazoles could also be differentiated by their IR spectra. The differentiation of both series was based upon the appearance of a weak, but distinct absorption band at 3160—3140 cm^{-1} in the spectra of 1,2,4-trisubstituted isomers (Table 1). Such a difference consistently occurred between isomers both in crystalline materials in KBr disks and in carbon tetrachloride or chloroform solution and therefore does not reflect the difference between their crystal structures. This absorption band was absent in 5-deuterio compounds (**4g**-d_1 and **4k**-d_1) and thus assigned to a C–H stretching vibration at the 5-position of imidazole ring shifted to higher frequencies than usual aromatic region[10] presumably by steric compression.

o-Hydroxybenzylideneamino compounds **4i** and **5d** exhibited internally bonded O–H stretching bands (centered at 3220 and 3170 cm^{-1}) at 4×10^{-3} M in carbon tetrachloride. This observation suggests that the *o*-hydroxyphenyl group and the imidazole ring must be in *E* configuration about the azomethine double bond to which they attached. Other **4** and **5** may also be *E* form in view of the similarities of UV spectra observed between the members of each series. If they were in *Z* configuration, R^1 should be twisted out of the plane of the rest of molecule as evidenced by examination of a scale model. Thus the UV spectra of 4-aryl series would resemble that of **4m** which lacks the longer-wavelength band (Table 4) due to the steric inhibition of conjugation between R^1 and the heteroaromatic ring caused by the α-methyl group (R^2=CH_3); on the other hand, the UV spectra of 5-aryl series would become comparable with those of **5g**.

In mass spectrometry, molecular ions were obtained for all 1-arylmethyleneamino compounds studied (Tables 1 and 2) and always represented the base peak. Primary fragmentation occurred at the N–N bond, leading to an intermediate, M^+–R^1R^2C=N (≃100%), common to the 1,2,4- and 1,2,5-isomers. Another ionization occurred to produce R^1R^2C=N^+=CS (≈60%) which is also common to both isomers. Thus practically identical spectra resulted between the members of each pair of isomers except for **4f** and **4j** in which fragmentation M^+–Cl· and M^+–MeO· occurred only in 4-aryl compounds as shown by the appropriate metastable ions. The R^4CN^+ ion, one of the criteria on which the structural assignment had been made in Ref. 1, was invariably found in the spectra of both isomers in comparable abundance (9—38%) and therefore of no diagnostic value for differentiation.

Although no reaction intermediates have been isolated in this study, a probable reaction mechanism that accounts for the results obtained here was represented in Fig. 2.

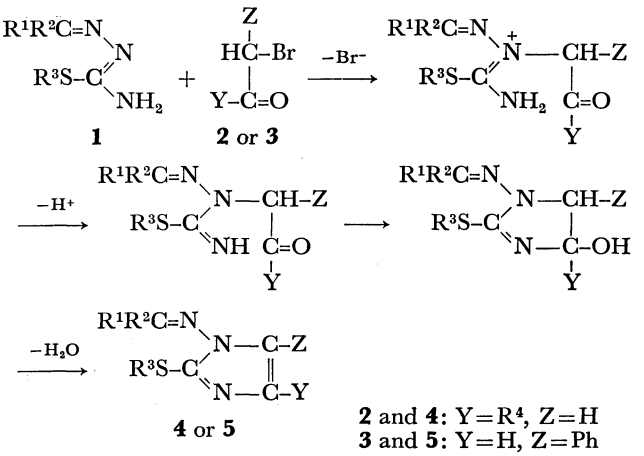


Fig. 2. A reaction mechanism for imidazole-ring formation.

The reaction should occur by the initial attack of N-2 which was believed to be the most nucleophilic center in **1**[11] on the α-carbon of **2** or **3**. An alternative path, in which the condensation of the terminal amino group of **1** with the carbonyl group of **2** or **3** is the first step, is unlikely to operate because the substitution of phenacyl chloride for **2a** resulted in substantial recovery of the starting materials under the same conditions. If the reaction proceeds through the latter path, there would accumulate an initial product, R^1R^2C=N–N=C(SR^3)–N=C(CH_2Cl)Ph, in the reaction mixture because of low reactivity of the halogen in phenacyl chloride.

Both 4- and 5-aryl-1*H*-imidazoles (**4** and **5**) were found to undergo reductive cleavage to 1-acetyl-4-aryl-1*H*-imidazoles (**6**), *N*-benzylacetamides (**10**), and thiols (**11**) upon stirring with acetic acid and zinc dust in the presence of acetic anhydride at room temperature. A possible product 1-acetyl-5-phenyl-1*H*-imidazole from **5a**, if any, may rapidly rearrange to a thermodynamically favorable 4-phenyl isomer through a reversible process of acetylation.[12] The benzylthio derivative (**4u**) was more resistant to the reduction than alkylthio compounds and prolonged reaction periods caused considerable formation of unidentifiable amorphous materials leading to a poor yield of **6**. The nitro group of **4d** was simultaneously reduced to give **6c**. The reduction of nitro group readily took place under the reaction conditions as evidenced by rapid disappearance of the red color due to this group prior to evolution of methanethiol and therefore a compound 1-acetyl-4-*p*-nitrophenyl-1*H*-imidazole could not be obtained by this process. The acetyl group at N-1 was susceptible to hydrolysis and partially splitted off in working up.

Two protons H-2 and H-5 on the imidazole ring of **6** appeared as two doublets with a coupling constant of 1.3 Hz at about δ 8.1 and 8.4 ppm in DMSO-d_6 due to cross-ring coupling. Peak assignment of these protons can unambiguously be made on the basis of the spectrum of 1-acetyl-4-phenyl-5-deuterio-1*H*-imidazole (**6a**-d_1) which lacks the upfield resonance. This is in accordance with the common practice of assigning H-2 to the most downfield resonance of 1-substituted imidazoles,[13] although H-2 is not always the most deshielded proton.[14]

Hydrolysis of the arylmethyleneamino to an amino group of **4g** or **4k** was unsuccessful either in aqueous ethanolic hydrogen chloride or sodium hydroxide solution at the reflux temperature over a period of 10 h with total recovery of the starting imidazoles (Table 5). The corresponding 5-phenyl isomers, however, underwent hydrolysis to an extent of 24 and 22%, respectively. Ortho substituents on the benzylideneamino group of **4** accelerated the rate of hydrolysis independently of whether it is electron-releasing or electron-withdrawing. No specific intramolecular catalysis[15] was observed. On the other hand, **4m** was hydrolyzed to 97% under the same conditions and the reaction was substantially completed within 30 minutes when the hydrolysis was carried out in concentrated hydrochloric acid at 130 °C. In view of these observations, the susceptibility to hydrolysis of arylmethyleneamino group directly reflects the diminished or inhibited conjugation between the azomethine double bond and the adjacent aromatic rings resulting from crowding around the double bond.

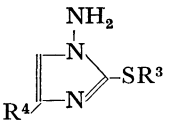
Hydrolytic products **7** and **9** could be obtained quantitatively by hydrazinolysis of **4** and **5**. When **4k** was heated with a large excess of hydrazine hydrate in

Table 5. Yield[a] of 1-aminoimidazoles from 1-arylmethyleneamino-2-methylthio-4- or 5-phenyl-1*H*-imidazoles

Substituents on the benzylideneamino group	4-Phenyl	5-Phenyl
o-Chloro	9	23
p-Chloro	0	24
o-Hydroxy	8	50
o-Methoxy	12	19
p-Methoxy	0	22
p-Methoxy-α-methyl	97	—

a) Estimated from NMR spectra after refluxing in aqueous ethanolic HCl for 10 h and evaporating under reduced pressure.

Table 6. 1-Amino-2-mercapto-4-aryl-1*H*-imidazoles



Compd No.	R^3	R^4	Yield (%)	Mp °C	Formula	Found (Calcd), % C	H	N	IR (KBr) νN–H[a]	NMR (CDCl$_3$), δ SCH_3	SCH_2	H-5
7a	Me	C_6H_5	98	122.5—123[b]	$C_{10}H_{11}N_3S$	58.55 (58.53)	5.43 (5.40)	20.35 (20.48)	3340—3100	2.59	—	7.20
7b	Me	*p*-$H_2NC_6H_4$	29	175—176[c]	$C_{10}H_{12}N_4S$	54.78 (54.54)	5.53 (5.49)	25.68 (25.44)	3350—3120	2.51	—	7.30[d]
7c	Me	*p*-ClC_6H_4	97[e]	138—139[f]	$C_{10}H_{10}ClN_3S$	50.08 (50.15)	4.28 (4.21)	17.53 (17.54)	3330—3140	2.64	—	7.30
7d	Me	*p*-$O_2NC_6H_4$	32	177.5—178[g]	$C_{10}H_{10}N_4O_2S$	48.18 (48.00)	4.00 (4.02)	22.18 (22.39)	3330—3130	2.62	—	7.96[d]
7e	*n*-Pr	C_6H_5	90[h]	79—80.5[i]	$C_{12}H_{15}N_3S$	61.91 (61.78)	6.47 (6.48)	17.87 (18.02)	3340—3140	—	3.04[j]	7.18
7f	H_2C=$CHCH_2$	C_6H_5	93	100—101[k]	$C_{12}H_{13}N_3S$	62.30 (62.32)	5.71 (5.67)	18.16 (18.17)	3350—3140	—	3.66[m]	7.19
7g	$C_6H_5CH_2$	C_6H_5	86	113—114[n]	$C_{17}H_{17}N_3S$	68.17 (68.31)	5.37 (5.38)	14.88 (14.94)	3320—3120	—	4.10	7.12

a) Composed of 4—5 bands, cm^{-1}. b) Lit,[18] mp 118 °C. c) Reddish beige plates from EtOH. d) In DMSO-d_6. e) Heated for 10 h. f) Colorless plates from EtOH. g) Yellowish orange needles from EtOH. h) Starting with **4s**. i) White needles from hexane. j) Triplet, J=6.8 Hz. k) Colorless needles from *i*-Pr_2O. *m*) Double triplet, J=6.5 and 0.8 Hz. n) Pale yellow prisms from EtOH.

2-methoxyethanol at 170 °C for 1.5 h, **7a** was obtained in 98% yield after isolation by means of column chromatography on silica gel. It was also possible to isolate and purify **7a** by extraction with methanol followed by recrystallization from benzene. In most cases, however, repeated recrystallizations were required to accomplish complete removal of azine **12** causing a considerable loss of the aminoimidazoles. The yields reported in Table 6 were those for a homogeneous fraction obtained by means of column chromatography except for **7b** and **7d**. 4-*p*-Nitrophenylimidazole **4d** gave **7b** in addition to the expected product **7d** as a result of simultaneous reduction of the nitro group. The treatment of **4t** with hydrazine hydrate was also complicated by concomitant reduction of the allyl to a propyl group, if the reaction mixture contained an acid or accidentally absorbed an acid vapor. The formation of **7e** reached the maximum 28.5% when 4 molar equivalents of acetic acid was present, while no reduction occurred in the absence of acid.[16] In contrast to certain methylthiotriazine derivatives,[6,17] nucleophilic attack by a hydrazine molecule on C-2 was not observed even after heating over a period of 10 h.

The aminoimidazoles **7** underwent deamination upon treatment with sodium nitrite in a hydrochloric acid–methanol mixture to give the corresponding 2,4-disubstituted imidazoles **8** in moderate yields. They were characterized by their IR spectra which exhibited a broad absorption band at 3060—2600 cm^{-1} due to the bonded N–H.

Pyl *et al.*[18] had reported a melting point of 118 °C for 1-amino-2-methylthio-4-phenyl-1*H*-imidazole. This value corresponds to that of **7a** but obviously not to 5-phenyl isomer **9**. The strength in support of the structure for **7a** may thus be obtained. However, there is no reason to believe it is the ring nitrogen which attacks the α-carbon of **2a** and not the amino nitrogen in the formation of the precursor 2-substituted 6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole by the reaction between 2-amino-1,3,4-thiadiazole and **2a**.[18] Consequently the practical agreement in the melting point of **7a** with that of the literature may be insufficient as the basis for determination of the substitution pattern of all the present 1,2,4- and 1,2,5-trisubstituted imidazoles.

Experimental

Melting points were determined in an open glass capillary and are uncorrected. IR spectra were recorded on a Hitachi EPI-G2 grating spectrophotometer. Spectra of solutions were obtained in 0.1-mm KBr or 5-mm KRS-5 cells and those of solid samples taken in KBr disks. UV spectra were recorded on a Hitachi EPS-2 spectrophotometer and mass spectra (75 eV) on a Japan Electron Optics JMS-OlS or JMS-D100 mass spectrometer using a direct inlet procedure. ^1H NMR spectra were obtained on a Nichiden-Varian T-60 or a Hitachi R-24 spectrometer, both operating at 60 MHz. Chemical shifts were reported in δ ppm downfield from internal tetramethylsilane. Following abbreviations were used: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad singlet, dt=double triplet, and vs=very strong.

α-Halo Carbonyl Compounds. Phenacyl bromides (**2a**—**2f**) were prepared from the corresponding acetophenones by the known methods[19] and **3** was obtained from phenylacetaldehyde according to the method described by Riehl.[20] NMR (CCl_4) 5.11 (d, 1, J=3.6 Hz, BrCH), 7.34 (s, 5, C_6H_5), 9.48 (d, 1, J=3.6 Hz, CHO). α-Ethoxyphenylacetaldehyde 2,4-dinitrophenylhydrazone,[21] mp 139 °C (lit,[22] mp 140 °C).

Isothiosemicarbazones. The compounds (**1a**—**1s**) were prepared by the procedure reported previously[11] with some appropriate modifications. New ones are: **1c**: white prisms (from hexane), mp 60—62 °C, yield 46%; NMR ($CDCl_3$) 2.51 (s, 3, SCH_3), 5.50 (br, 2, NH_2), 7.15—8.15 (m, 4, ring protons), 8.80 (s, 1, CH=N). Found: C, 47.37; H, 4.40; N, 18.42%. Calcd for $C_9H_{10}ClN_3S$: C, 47.47; H, 4.43; N, 18.45%. **1d**: pale yellow prisms (from *i*-PrOH), mp 98—100 °C, yield 49%; NMR ($CDCl_3$) 2.49 (s, 3, SCH_3), 5.50 (br, 2, NH_2), 7.33 (d, 2, J=8.5 Hz, ring protons), 7.66 (d, 2, J=8.5 Hz, ring protons), 8.33 (s, 1, CH=N). Found: C, 47.16; H, 4.38, N, 18.39%. Calcd for $C_9H_{10}ClN_3S$: C, 47.47; H, 4.43; N, 18.45%. **1e**[23]: yellow plates (from aq EtOH), mp 140—142 °C, yield 81%; NMR ($CDCl_3$) 2.48 (s, 3, SCH_3), 2.98 (s, 6, $N(CH_3)_2$), 5.40 (br, 2, NH_2), 6.68 (d, 2, J=9.6 Hz, ring protons), 7.62 (d, 2, J=9.6 Hz, ring protons), 8.32 (s, 1, CH=N). Found: C, 55.92; H, 6.70; N, 23.65%. Calcd for $C_{11}H_{16}N_4S$: C, 55.91; H, 6.83; N, 23.72%. **1f**: faintly yellow needles (from aq EtOH), mp 162.5—163 °C, yield 78%; NMR ($CDCl_3$–DMSO-d_6, 4:1 by volume) 2.45 (s, 3, SCH_3), 6.25 (br, 2, NH_2), 6.70—7.50 (m, 4, ring protons), 8.22 and 8.37 (two s, 0.5, 0.5, CH=N), 11.15 and 11.46 (two br, 0.5, 0.5, OH).[24] Found: C, 51.72; H, 5.32; N, 19.95%. Calcd for $C_9H_{11}N_3OS$: C, 51.67; H, 5.30; N, 20.09%. **1g**: white needles (from hexane), mp 58.5—59 °C, yield 90%; NMR ($CDCl_3$) 2.49 (s, 3, SCH_3), 3.82 (s, 3, OCH_3), 5.50 (br, 2, NH_2), 6.80—8.10 (m, 4, ring protons), 8.78 (s, 1, CH=N). Found: C, 54.08; H, 5.99; N, 18.73%. Calcd for $C_{10}H_{13}N_3OS$: C, 53.80; H, 5.87; N, 18.83%. **1p**: white plates (from hexane), mp 67—68 °C, yield 65%; NMR ($CDCl_3$) 1.10 (t, 3, J=7.4 Hz, CCH_3), 2.36 (m, 2, CH_2), 2.42 (s, 3, SCH_3), 5.36 (br, 2, NH_2), 7.73 (t, 1, J=5.0 Hz, CH=N). Found: C, 41.62; H, 7.52; N, 28.95%. Calcd for $C_5H_{11}N_3S$: C, 41.37; H, 7.64; N, 28.95%. **1q**: white needles (from hexane), mp 82—83 °C, yield 83% NMR ($CDCl_3$) 1.13 (t, 3, J=7.4 Hz, CCH_3), 2.35 (m, 2, CCH_2), 4.22 (s, 2, SCH_2), 5.30 (br, 2, NH_2), 7.30 (s, 4, ring protons), 7.80 (t, 1, J=5.1 Hz, CH=N). Found: C, 51.93; H, 5.49; N, 16.38%. Calcd for $C_{11}H_{14}ClN_3S$: C, 51.66; H, 5.52; N, 16.43%. **1s**: pale yellow plates (from hexane), mp 77.5—78 °C, yield 63%; NMR ($CDCl_3$) 2.00 (s, 3, CCH_3), 2.01 (s, 3, CCH_3), 4.23 (s, 2, SCH_2), 5.14 (br, 2, NH_2), 7.25 (s, 4, ring protons). Found: C, 51.32; H, 5.50; N, 16.49%. Calcd for $C_{11}H_{14}ClN_3S$: C, 51.66; H, 5.52; N, 16.43%.

Preparation of 4k (a typical example). A mixture of **1h** (0.56 g, 2.5 mmol), **2a** (0.60 g, 3.0 mmol), sodium hydrogencarbonate (0.63 g, 7.5 mmol), and MeCN (3 ml) was heated under stirring at 75 °C for 3 h. After cooling, the solids were filtered off, washed with cold MeCN, and then suspended in sufficient water to dissolve any inorganic salts. The insoluble crystals were collected on a filter, washed with water, and then dried to give **4k** (0.60 g, 75%), mp 169—169.5 °C. Recrystallization from benzene–EtOH did not raise the melting point, but resulted in improvement in the appearance of the crystal. When 0.75 g (3.75 mmol) of **2a** was used, the yield of **4k** increased to 0.65 g (80.3%). The 5-deuterio derivative (**4k**-d_1) was similarly prepared by substituting phenacyl-*methylene*-d_2 bromide ($C_6H_5COCD_2Br$), which in turn was obtained by brominating acetophenone-α,α,α-d_3 ($C_6H_5COCD_3$), for **2a** in 65% yield. Pale yellow needles (benzene–EtOH), mp 168—169 °C not depressed by **4k**. IR ($CHCl_3$) 2340 (C–D) cm^{-1}; NMR ($CDCl_3$) 2.70 (s, 3, SCH_3), 3.78 (s, 3, OCH_3), 6.87 (d,

2, J=8.7 Hz, *p*-methoxyphenyl protons), 7.21 (m, 3, $H^{m,p}$ of 4-phenyl), 7.63 (d, 2, J=8.7 Hz, *p*-methoxyphenyl protons), 7.69 (m, 2, H^{o} of 4-phenyl), 8.10 (s, 1, CH=N); M^+ 324 (M 324). Similarly, **4g**-d_1 was obtained in 64% yield as yellow needles, mp 173.5—174 °C. IR ($CHCl_3$) 2340 (C–D) cm^{-1}; NMR ($CDCl_3$) 2.67 (s, 3, SCH_3), 7.26 (m, 3, $H^{m,p}$ of 4-phenyl), 7.31 (d, 2, J=8.5 Hz, *p*-chlorophenyl protons), 7.65 (d, 2, J=8.5 Hz, *p*-chlorophenyl protons), 7.70 (m, 2, H^{o} of 4-phenyl), 8.08 (s, 1, CH=N); M^+ 328 (M 328).

Preparation of **5c** *(a typical example).* To a warm soln of **3** (0.5 g, 2.5 mmol) in MeCN (5 ml) was added **1d** (1.14 g, 5.0 mmol) and quickly dissolved with agitation. The reaction mixture solidified within a few min. After heating for 1 h at 83 °C, the solids were filtered off, washed with MeCN and then Et_2O. The filtrate and the washings were combined and evaporated. The residual liquid was dissolved in benzene (30 ml) and the soln was washed with 0.1 M hydrochloric acid and then with water. The organic layer was dried over anhyd. sodium sulfate and evaporated. The residue (0.73 g) was charged onto a silica gel column (40 g) and eluted by benzene–EtOH (98: 2 by volume). A homogeneous fraction (0.43 g, 52.4%) was crystallized from *i*-PrOH (0.5 ml) to give **5c** as bright yellow needles, mp 96—97 °C. Recrystallization from *i*-PrOH (1.0 ml) yielded yellow needles, mp 96.5—97 °C. NMR ($CDCl_3$) 7.45 (d, 2, J=8.0 Hz, *p*-chlorophenyl), 7.70 (d, 2, J=8.0 Hz, *p*-chlorophenyl), 8.22 (s, 1, CH=N).

Preparation of **5g**. A mixture of **1p** (0.73 g, 5.0 mmol), **3** (1.00 g, 5.0 mmol), sodium hydrogencarbonate (1.70 g, 20 mmol), and MeCN (10 ml) was stirred at 74 °C for 3 h and then filtered. After the inorganic salts were washed with MeCN, the filtrate and the washings were evaporated and the residue taken up in benzene (30 ml). When the soln was worked up in a similar manner to the preparation of **5c**, there was obtained **5g** as pale yellow prisms (0.19 g, 15%), mp 38—39.5 °C. NMR ($CDCl_3$) 1.11 (t, 3, J=7.0 Hz, CCH_3), 2.40 (m, 2, CH_2), 7.60 (t, 1, J=4.8 Hz, CH=N).

Reaction of **1p** *with* **2a**. A mixture of **1p** (0.73 g, 5 mmol), **2a** (1.0 g, 5 mmol), sodium hydrogencarbonate (1.7 g, 20 mmol), and MeCN (10 ml) was stirred at 75 °C for 3 h. The inorganic salts were filtered off and washed with benzene. The filtrate and the washings were combined and evaporated. The residue (1.41 g) was charged onto silica gel column (100 g) and eluted with benzene–EtOH (98: 2 by volume). Two fractions, an imidazole-rich fraction (0.53 g) containing a small amount of methyl phenyl sulfide and a triazine-rich fraction (0.17 g) were separated. The former was again subjected to column chromatography under the same conditions to give pure **4w** as a yellow oil (0.33 g, 27%). UV_{max} (MeOH) 254 (ε 20 100), 271 (ε 15 900), 311 (ε 8 300) nm; NMR ($CDCl_3$) 1.19 (t, 3, J=7.0 Hz, CCH_3), 2.52 (m, 2, CH_2), 2.70 (s, 3, SCH_3), 7.56 (s, 1, H-5), 7.79 (t, 1, J=4.8 Hz, CH=N). The perchlorate was prepared in a conventional manner; IR (KBr) 3170 (NH^+), 1100 *vs.* (ClO_4^-) cm^{-1}. The mixed melting point with a product prepared by reacting **7a** with propionaldehyde and salt-forming with perchloric acid did not show any depression (179.5 °C). The triazine-rich fraction was crystallized from *i*-PrOH (0.5 ml) to afford **15a** as pale yellow prisms (0.06 g), mp 99—99.5 °C (lit,[6] mp 99—100.5 °C); NMR ($CDCl_3$) 2.71 (s, 3, SCH_3), 7.52 (m, 3, $H^{m,p}$ of 5-phenyl), 8.10 (m, 2, H^{o} of 5-phenyl), 9.33 (s, 1, H-6). (Found: N, 20.97%). Methyl phenacyl sulfide separated from the imidazole-rich fraction exhibited the identical IR and NMR spectra with those of an authentic sample which was prepared by introducing methanethiol generated from a mixture of **14** (R^3=Me, as a sulfate) and aq sodium hydroxide into a soln of **2a** in Et_2O. 2,4-Dinitrophenylhydrazone: mp 164—165 °C (lit,[25] mp 164—165.5 °C).

Reaction of **1r** *with* **2a**. A solution of **1r** (10.0 g, 69 mmol) and **2a** (6.86 g, 34.5 mmol) in EtOH (100 ml) was heated at 70—75 °C for 3 h and then evaporated. The residue was taken up in chloroform and the soln was repeatedly washed with water acidified to pH 5 with hydrobromic acid. The organic layer was dried over anhyd. sodium sulfate and evaporated. The residue (6.69 g) was triturated with six 75 ml-portions of a hexane–diisopropyl ether mixture (2: 1 by volume) and the combined extracts were evaporated to give an oil (4.96 g). From a one-gram portion of this oil, there were separated **15a** (0.28 g, 20%), mp 95—98 °C; **4z** (0.13 g, 7.5%), NMR ($CDCl_3$) 1.90 (s, 3, CCH_3), 2.20 (s, 3, CCH_3), 2.61 (s, 3, SCH_3), 7.17 (s, 1, H-5), 7.35 (m, 3, $H^{m,p}$ of 4-phenyl), 7.80 (m, 2, H^{o} of 4-phenyl), perchlorate mp 180—180.5 °C, IR (KBr) 3180 (NH^+), 1120 (ClO_4^-) cm^{-1}; and impure **7a** (0.22 g). Ammonium bromise (0.38 g) and **14** (R^3=CH_3) as a picrate (1.0 g), mp 220 °C dec, not depressed on mixing with an authentic sample, were isolated from the aq washings. When **1s** was react d with **2a** by this method, **15c** was obtained in 38% yield and no imidazole was detected. Deep yellow powder (from EtOH), mp 115—116 °C; IR (KBr) 1540, 1500, 1250, 760 cm^{-1}; NMR ($CDCl_3$) 4.50 (s, 2, CH_2), 7.35 (m, 4, *p*-chlorophenyl protons), 7.55 (m, 3, $H^{m,p}$ of 5-phenyl), 8.10 (m, 2, H^{o} of 5-phenyl), 9.35 (s, 1, H-6). Found: C, 61.07; H, 3.92; N, 13.36%. Calcd for $C_{16}H_{12}ClN_3S$: C, 61,24; H, H, 3.80; N, 13.40%.

Reaction of **1r** *with* **2c**. A mixture of **1r** (1.45 g, 10 mmol), **2c** (3.50 g, 15 mmol), sodium hydrogencabronate (5.0 g, 60 mmol), and MeCN (20 ml) was heated at 80 °C under stirring for 5 h and the inorganic salts were filtered off. After the filtrate was evaporated, the residue was worked up by the same manner as that in the reaction with **2a** giving a hexane–diisopropyl ether extract (1.35 g) from which **15b** (0.18 g, 7.6%) was isolated by crystallization from *i*-PrOH. It was passed a silica gel column using chloroform as an eluent and the homogeneous fraction recrystallized from aq EtOH to afford yellow needles, mp 164—164.5 °C (lit,[7] mp 163 °C); NMR ($CDCl_3$) 2.71 (s, 3, SCH_3), 7.51 (d, 2, J=9.0 Hz, *p*-chlorophenyl protons), 8.12 (d, 2. J=9.0 Hz, *p*-chlorophenyl protons), 9.34 (s, 1, H-6). (Found: C, 50.46; H, 3.48; N, 17.80%). The mother liquor obtained after removal of **15b** was heated under reflux in EtOH (7 ml) containing concentrated hydrochloric acid (0.5 ml) and anisaldehyde (0.5 ml) for 30 min. When the reaction mixture was made basic (pH 9) with aq ammonia **4o** (0.57 g, 16%) precipitated. When **1r** (1.45 g, 10 mmol) was reacted with **2c** (1.17 g, 5 mmol) by heating in ethanolic soln at 65 °C for 4 h, there were obtained **15b** (0.33 g, 28%) and **4o** (0.30 g, 17%).

Reductive Cleavage of **4b** *(a typical example).* A mixture of **4b** (0.66 g), zinc dust (13.0 g), glacial acetic acid (42 ml), and acetic anhydride (21 ml) was stirred at room temperature for 3 h, filtered, and the filtrate was evaporated to give a residue which was then triturated with water (10 ml). The insoluble solid was collected by filtration, washed with water and then dried in vacuo giving **6b** (R^4=*p*-ClC_6H_4) (0.36 g, 82%), mp 180—183 °C. Recrystallization from EtOH yielded lustrous flat prisms. mp 186.5 °C. IR(KBr) 3140 (νC–H), 1720 *vs.* (C=O), 835 (δC–H) cm^{-1}. NMR (DMSO-d_6) 2.64 (s, 3, $COCH_3$), 7.39 (d, 2, J=8.2 Hz, *p*-chlorophenyl protons), 7.84 (d, 2, J=8.2 Hz, *p*-chlorophenyl protons), 8.17 (d, 1, J=1.3 Hz, H-5), 8.41 (d, 1, J=1.3 Hz, H-2). Found: C, 59.68; H, 4.00; N, 12.70%. Calcd for $C_{11}H_9ClN_2O$: C, 59.88; H, 4.11; N, 12.69%. The product (0.1 g) was hydrolyzed by refluxing in an EtOH–hydrochloric acid mixture to 4-*p*-chlorophenylimidazole hydro-

chloride which was then treated with aq sodium hydroxide soln and the free base (0.07 g, 87%) recrystallized from water affording 4-*p*-chlorophenylimidazole, mp 146—147 °C (lit,[26] mp 145—147 °C). IR(KBr) 3130—2600 *vs.* (N–H) cm^{-1}.

The following compounds were similarly obtained: **6a** ($R^4=C_6H_5$) from **4k** in 38% yield, mp 148—149 °C (lit,[27] mp 153 °C). IR (KBr) 1725 *vs.* (C=O) cm^{-1}; NMR (DMSO-d_6) 2.65 (s, 3, $COCH_3$), 7.32 (m, 3, $H^{m,p}$ of 4-phenyl), 7.81 (m, 2, H^o of 4-phenyl), 8.10 (d, 1, J=1.3 Hz, H-5), 8.38 (d, 1, J=1.3 Hz, H-2). (Found: N, 14.99%). 4-Phenylimidazole which was contained in the aq washings of **6a** was separated as picrate in 19% yield, mp 214—215 °C lit,[27] mp 215 °C). (Found: C, 48.17; H, 2.96; N, 18.77%). 1-Acetyl-4-phenyl-1*H*-imidazole was also obtained from **5a** in 55% yield, mp 149 °C not depressed by **6a** from **4k**. The 5-deuterio compound **4k**-d_1 gave **6a**-d_1 in 62% yield, mp 146—147 °C. IR(KBr) 1725 *vs.* (C=O) cm^{-1}; NMR (DMSO-d_6) 2.66 (s, 3, $COCH_3$), 7.30 (m, 3, $H^{m,p}$ of 4-phenyl), 7.82 (m, 2, H^o of 4-phenyl), 8.38 (s, 1, H-2). **6c** (R^4=*p*-AcNH-C_6H_4) from **4d** in 74% yield as colorless prisms, mp 258 °C (from AcOH–Ac_2O); IR(KBr) 1735 *vs.* (C=O), 1680 (C=O) cm^{-1}; NMR (CF_3CO_2D) 2.50 (s, 3, $COCH_3$), 2.91 (s, 3, $COCH_3$), 7.72 (s, 4, C_6H_4), 8.12 (d, 1, J=1.6 Hz, H-5), 9.29 (d, 1, J=1.6 Hz, H-2). Found: C, 64.30; H, 5.35; N, 17.13%. Calcd for $C_{13}H_{13}N_3O_2$: C, 64,18; H, 5.39; N, 17.27%. Selective hydrolysis at N-1 of **6c** was accomplished by agitating in water adjusted to pH 11 at room temperature and afforded 4-*p*-acetamidophenylimidazole, mp 250—250.5 °C (lit,[28] mp 250—251 °C); IR (KBr) 1685 cm^{-1} (C=O). (Found: C, 65.49; H, 5.50; N, 20.98%). **6d** (R^4=*p*-$MeOC_6H_4$) from **4c** in 78% yield as colorless needles, mp 184.5—185 °C (from EtOH); IR (KBr) 3140 (νC–H), 1730 *vs.* (C=O), 840 (δC–H) cm^{-1}; NMR (DMSO-d_6) 2.65 (s, 3, $COCH_3$). 3.78 (s, 3, OCH_3), 6.93 (d, 2, J=8.7 Hz, *p*-methoxyphenyl protons), 7.77 (d, 2, J=8.7 Hz, *p*-methoxyphenyl protons), 8.02 (d, 1, J=1.3 Hz, H-5), 8.37 (d, 1, J=1.3 Hz, H-2). Found: C, 66.45; H, 5.54; N, 12.98%. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96%. It was hydrolyzed to 4-*p*-methoxyphenylimidazole (75%), mp 137.5—138 °C (lit,[28] mp 136—137 °C); IR (KBr) 3100—2600 *vs.* (N–H) cm^{-1}. (Found: C, 68.92; H, 5.81; N, 16.25%).

Reductive Cleavage of 4k (another example for isolation of the cleaved products). A mixture of **4k** (0.7 g), zinc dust (18 g), glacial acetic acid (70 ml), and acetic anhydride (28 ml) was stirred at room temperature for 2 h, filtered, and the filtrate was evaporated. The residue was heated with a mixture of water (10 ml) and MeOH (5 ml) and the aq extract was treated with a soln of picric acid (0.5 g) in water (30 ml) giving 4-phenylimidazole picrate (0.55 g, 69%). The mother liquor of picrate was evaporated and the residue was extracted with chloroform (50 ml). The extract was washed successsively with aq ammonia and water and then evaporated to afford **10** (R^1=*p*-$MeOC_6H_4$, R^2=H), mp 95—96 °C (0.35 g, 90%) (lit,[29] mp 95.5—97 °C). IR (KBr) 3250 (N–H), 1630 (C=O), 1255 (C–O–C) cm^{-1}; NMR ($CDCl_3$) 1.95 (s, 3, $COCH_3$), 3.74 (s, 3, OCH_3), 4.25 (d, 2, J=6.0 Hz, NCH_2), 6.30 (br, 1, NH), 6.77 (d, 2, J=8.3 Hz, ring protons), 7.12 (d, 2, J=8.3 Hz, ring protons). In the same manner, **4s**, **4t**, and **4u** gave 4-phenylimidazole picrate in 87, 73, and 17% yields, respectively.

Hydrazinolysis of 4k (a typical example). A mixture of **4k** (0.24 g), 80% hydrazine hydrate (0.5 ml), and 2-methoxyethanol (2 ml) was heated to 165°C for 70 min and then evaporated. The residue was charged onto a silica gel column (30 g), eluted with chloroform, and the homogeneous fraction was evaporate giving practically pure **7a** (0.15 g, 98%), mp 119—120 °C. Recrystallization from benzene gave colorless needles, mp 122.5—123 °C. UV_{max} (MeOH) 271 nm (ε 16 900); NMR ($CDCl_3$) 4.70 (br, 2, NH_2), 7.30 (m, 3, $H^{m,p}$ of 4-phenyl), 7.71 (m, 2, H^o of 4-phenyl). From a fraction which preceded **7a**, there was obtained **12** (R^1=*p*-$MeOC_6H_4$, R^2=H), mp 167—169 °C (from benzene) (turned to a clear melt at 179—180 °C) (lit,[30] mp 167—163 °C). (Found: C, 71.78; H, 6.02; N, 10.31%). Alternatively, the residue obtained after evaporation of the reaction mixture was triturated with water and the insoluble solids were heated with MeOH at the reflux temperature for 30 min. Insoluble **12** was filtered off and the filtrate evaporated to give a residue which was then recrystallized from benzene affording **7a** (54%), mp 122—123 °C. According to the latter procedure, **5a** yielded **9** (74%) as colorless needles, mp 141—142 °C. UV_{max} (MeOH) 278 nm (ε 16 800); IR (KBr) 3340 and 3100 (NH) cm^{-1}; NMR ($CDCl_3$) 2.59 (s, 3, SCH_3), 4.55 (br, 2, NH_2), 7.00 (s, 1, H-4), 7.35 (s, 5, C_6H_5). Found: C, 58.75; H, 5.40; N, 20.66%; M^+, 205. Calcd for $C_{10}H_{11}N_3S$: C, 58.53; H, 5.40; N, 20.48%; M, 205.

Hydrazinolysis of 4d. A mixture of **4d** (0.86 g), 80% hydrazine hydrate (7.5 ml), and 2-methoxyethanol (7.5 ml) was heated to 175 °C for 13 h[31] and then evaporated. The residual liquid was triturated with EtOH (6 ml) to crystallize **7d** (0.13 g, 20%), mp 177.5—178 °C (from EtOH). NMR (DMSO-d_6) 6.06 (br, 2, NH_2), 8.00 (d, 2, J=9.1 Hz, *p*-nitrophenyl protons), 8.23 (d, 2, J=9.1 Hz, *p*-nitrophenyl protons). The mother liquor after crystallization of **7d** was allowed to stand overnight and deposited **7b** (0.16 g, 29%) was collected by filtration, mp 175—176 °C (from EtOH). NMR (DMSO-d_6) 3.67 (br, NH_2), 5.88 (br, 2, NH_2), 6.54 (d, 2, J=8.6 Hz, *p*-aminophenyl protons), 7.38 (d, 2, J=8.6 Hz, *p*-aminophenyl protons). When the reaction was carried out by heating a mixture of **4d** (0.68 g), 80% hydrazine hydrate (6 ml), and 2-methoxyethanol (24 ml) for 2 h (**4d** had dissolved within 10 min) and concentrating the mixture to one half of the original volume, **7d** gradually crystallized (0.16 g, 32%), mp 177—178 °C.

Hydrolysis of 4m. A soln of **4m** (0.92 g) in concentrated hydrochloric acid (20 ml) was heated to 130 °C for 30 min and the separated *p*-methoxyacetophenone (0.4 g, 98%) was removed by extraction with Et_2O. The aq layer was diluted with water (7 ml), made basic with aq ammonia, and extracted with chloroform (30 ml) giving **7a** (0.44 g, 79%), mp 120—122 °C.

Deamination of 7. To a stirred mixture of **7a** (0.41 g), concentrated hydrochloric acid (4 ml), and MeOH (4 ml) was added a soln of sodium nitrite in water (0.1 g/ml) until an excess of nitrous acid remained after the last addition. Stirring was continued for 4 h at room temperature and the mixture was made alkaline (pH 10) with aq soln of sodium hydroxide. The solid was filtrered and washed with water giving **8a** (R^3=Me, $R^4=C_6H_5$) (0.26 g, 68%), mp 137—138 °C (lit,[32] mp 135.5—136.5 °C). IR (KBr) 3060—2600 (N–H) cm^{-1}. The following compounds were similarly obtained: **8b** (R^3=Me, R^4=*p*-ClC_6H_4): colorless plates (from *i*-PrOH), 84%, mp 181—182 °C; IR (KBr) 3050—2580 (N–H) cm^{-1}; NMR ($CDCl_3$) 2.64 (s, 3, SCH_3), 5.64 (br, 1, NH), 7.28 (d, 2, J=8.9 Hz, *p*-chlorophenyl protons), 7.36 (s, 1, H-4 or 5), 7.70 (d, 2, J=8.9 Hz, *p*-chlorophenyl protons). Found: C, 53.34; H, 4.08; N, 12.27%. Calcd for $C_{10}H_9ClN_2S$: C, 53.45; H, 4.04; N, 12.47%. **8c** (R^3=Me, R^4=*p*-$O_2NC_6H_4$): bright yellow needles (from benzene–MeOH), 47%, mp 211—212 °C; IR (KBr) 3140—2590 (N–H) cm^{-1}; NMR (CF_3CO_2D) 2.91 (s, 3, SCH_3), 7.88 (s,

1, H-4 or 5), 7.95 (d, 2, J=9.2 Hz, *p*-nitrophenyl protons), 8.48 (d, 2, J=9.2 Hz, *p*-nitrophenyl protons). Found: C, 51.24; H, 3.87; N, 18.03%. Calcd for $C_{10}H_9N_3O_2S$: C, 51.06; H, 3.86; N, 17.87%. **8d** (R^3=*n*-C_3H_7, R^4=C_6H_5): 48%, mp 79.5—80 °C (lit,[32] mp 78—79 °C), IR (KBr) 3050—2600 (N–H) cm^{-1}. (Found: C, 66.07; H, 6.53; N, 12.57%). **8e** (R^3=H_2C=$CHCH_2$, R^4=C_6H_5): colorless needles (from *i*-Pr_2O–hexane), 62%, mp 93—94 °C; IR (KBr) 3060—2550 (N–H) cm^{-1}; NMR ($CDCl_3$) 3.55 (dt, 2, J= 6.8 and 0.9 Hz, SCH_2), 5.00 (m, 2, =CH_2), 5.80 (m, 1, –CH=), 7.23 (m, 3, $H^{m,p}$ of phenyl), 7.32 (s, 1, H-4 or 5), 7.64 (m, 2, H^o of phenyl), 10.43 (s, 1, NH). Found: C, 66.56; H, 5.68; N, 12.73%. Calcd for $C_{12}H_{12}N_2S$: C, 66.65; H, 5.59; N, 12.96%. **8f** (R^3=$C_6H_5CH_2$, R^4=C_6H_5): 19%, mp 175—176 °C (lit,[4] mp 176.5—177.5 °C); IR (KBr) 3050—2580 (N–H) cm^{-1}. (Found: C, 72.00; H, 5.46; N, 10.30%).

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