weakly basic N-methylarylamines should be investigated. Among polynitro-N-methylanilines it is not known whether a nitro group at the 2- or 6-position is necessary. There may be others which do not fit the projected scheme. Nevertheless, coupled with other physical methods, the procedure could be helpful in the identification of compounds having an N-methyl group as part of the molecule.

The Ionization Constants of Some 4,5-Substituted 2-Methylpyrimidines

SATOSHI MIZUKAMI AND EIZO HIRAI

Shionogi Research Laboratory, Shionogi and Company, Ltd., Fukushima-ku, Osaka, Japan

Received September 28, 1965

An extension of the Hammett's equation to pyrimidines is attempted. The basic ionization constants of 4,5-substituted 2-methylpyrimidines are determined potentiometrically or spectrophotometrically. The base strengths are proportional to σ_m (for 5-substituent) and σ_p (for 4-substituent) values. A method is developed for the use of the Hammett's equation in the elucidation of the amino–imino tautomerism and the protonation equilibrium of 4-aminopyrimidines.

Hammett's equation[1] has played an important part in the investigation of the equilibrium and the mechanism of the reactions for benzene derivatives. Jaffé[2] and Imoto, *et al.*[3] found that this equation could be extended to heterocyclic compounds, such as pyridines, thiophenes, and furans, which have an aromatic structure of six π electrons, without modification. The application of this equation to pyrimidines, however, has never been examined. The authors have carried out the present study in order to extend this equation to the base strength of pyrimidines. Although the basic ionization constants of a number of pyrimidines have been reported,[4,5] there is little data for pyrimidines having a substituent attached to the 5-position in the nucleus. For this purpose we have measured the basic ionization constants of a series of 5-substituted 2-methylpyrimidines having an amino, a dimethylamino, or an alkoxyl group at the 4-position.

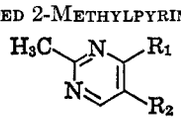
The 4-aminopyrimidines may exist as a corresponding 4-iminodihydropyrimidine resulting from the amino–imino tautomerism.[6] Brown and co-workers[7] have already presented spectroscopic evidence that 4-aminopyrimidine exists largely as the amino form in water. However, little attention has been paid to the effect of substituents on the tautomerism. We shall first examine if their conclusion is universally applicable to 5-substituted 4-amino-2-methylpyrimidines.

Results and Discussion

The basic ionization constants of the pyrimidines studied were determined by potentiometric and spectrophotometric methods, and the thermodynamic corrections[5] were made. The corrected pK_a values are reported in Table I. Plots of the values for the 4-amino- and 4-dimethylamino-2-methylpyrimidines *vs.* the *meta*-substituent constants (σ_m values) are given in Figure 1. The σ_m values are used as a measure of the polar effect of the substituents at the 5-position of the pyrimidines. Figure 1 reveals that for each series of the 4-aminopyrimidines and the 4-dimethylaminopyrimidines, a linear correlation exists between pK_a and σ_m without modification. Table II lists the reaction constants (ρ values) and the intercepts of the lines in Figure 1.

TABLE I

THE BASIC IONIZATION CONSTANTS OF 4,5-SUBSTITUTED 2-METHYLPYRIMIDINES AT 25°



No.	R_1	R_2	pK_a (method)[a]	σ_p[b] (for R_1)	σ_m[b] (for R_2)	$\Sigma\sigma$
1	NH_2	H	6.53 (P)	−0.66	0.00	−0.66
2	NH_2	$CONH_2$	4.97 (P)	−0.66	0.28[c]	−0.38
3	NH_2	COOH	2.14 (S)	−0.66	0.37	−0.29
4	NH_2	$COOC_2H_5$	4.53 (P)	−0.66	0.37	−0.29
5	NH_2	CHO	4.46 (P)	−0.66	0.381[d]	−0.28
6	NH_2	CN	3.51 (S)	−0.66	0.56	−0.10
7	$N(CH_3)_2$	H	7.49 (P)	−0.83	0.00	−0.83
8	$N(CH_3)_2$	$CONH_2$	5.93 (P)	−0.83	0.28[c]	−0.55
9	$N(CH_3)_2$	COOH	1.90 (S)	−0.83	0.37	−0.46
10	$N(CH_3)_2$	$COOC_2H_5$	5.54 (P)	−0.83	0.37	−0.46
11	$N(CH_3)_2$	CN	4.37 (P)	−0.83	0.56	−0.27
12	$NHCOCH_3$	$COOC_2H_5$	1.43 (S)	0.00	0.37	0.37
13	OC_2H_5	$COOC_2H_5$	2.70 (S)	−0.24	0.37	0.13
14	OCH_3	H	3.98 (S)	−0.268	0.00	−0.268
15	OCH_3	OCH_3	4.11 (P, S)	−0.268	0.115	−0.153
16	$OCH(CH_3)_2$	H	4.46 (P)	−0.286[c]	0.00	−0.268
17	OC_6H_5	H	3.17 (S)	−0.028[c]	0.00	−0.028

[a] P, potentiometric method; S, spectrophotometric method. [b] Most of the σ values were those given by D. H. McDaniel and H. C. Brown [*J. Org. Chem.*, **23**, 420 (1958)]. [c] σ values were given by H. H. Jaffé.[9] [d] Reference 1.

For a series of 4-aminopyrimidines, if the amino–imino tautomerism is present, the protonation equilibria may be drawn as shown in Scheme I; that is, IIIa–VIIb may be assumed for the protonated cationic structure. For a series of 4-dimethylaminopyrimidines which necessarily possess the amino structure, only A and B in Scheme I need be considered for the protonation equilibria. The success of the Hammett

(1) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p 184.

(2) H. H. Jaffé and G. O. Doak, *J. Am. Chem. Soc.*, **77**, 4441 (1955).

(3) (a) E. Imoto, Y. Ohtsuji, T. Hirai, H. Inoue, R. Motoyama, and H. Kakiuchi, *Nippon Kagaku Zasshi*, **77**, 804 (1956); (b) R. Motoyama, J. Ogawa, and E. Imoto, *ibid.*, **78**, 962 (1957); (c) Y. Ohtsuji, T. Kimura, Y. Sugimoto, E. Imoto, H. Omori, and T. Ohgawara, *ibid.*, **80**, 1021 (1959); (d) Y. Ohtsuji, Y. Koda, E. Imoto, K. Kubo, and M. Furukawa, *ibid.*, **81**, 1293 (1959).

(4) D. J. Brown, "Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, p 464.

(5) A. Albert, "Physical Methods in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky, Ed., Academic Press Inc., New York, N., Y., 1963, p 1.

(6) G. W. Kenner and A. R. Todd, "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p 258.

(7) D. J. Brown, H. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 1294 (1956).

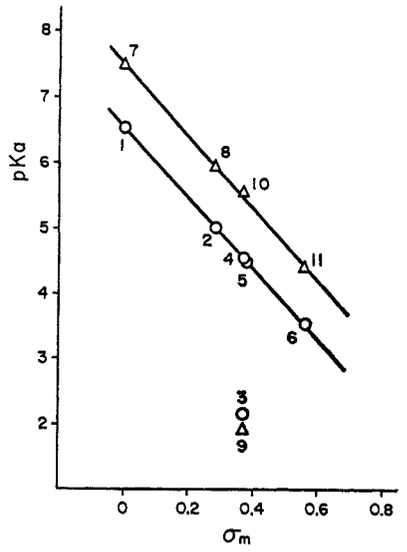


Figure 1.—Variation of pK_a with σm for pyrimidines; O, 5-substituted 4-amino-2-methyl-; Δ, 5-substituted 4-dimethylamino-2-methyl.

TABLE II

THE REACTION CONSTANTS AND INTERCEPTS FOR HAMMETT PLOTS OF THE 2-METHYLPYRIMIDINE BASICITIES[a]

Series	ρ value	Intercept (pK_a)	r[b]	Std dev	n[c]
5-Substituted 4-amino-	5.389	6.515	0.9998	0.04	5
5-Substituted 4-dimethylamino-	5.525	7.507	0.999	0.07	4
4,5-Substituted	5.014	3.124	0.993	0.19	15

[a] The values calculated do not include data for the 5-carboxy derivatives. [b] The correlation coefficient. [c] The number of compounds involved in the calculation of the ρ values.

equation for each series, however, indicates that an actual proton acceptor in the pyrimidine molecules is not the 4-amino or 4-dimethylamino group, but is the nuclear nitrogen *meta* to the 5-substituent.[8] Accordingly, the protonation equilibrium of 5-substituted 4-dimethylamino-2-methylpyrimidines is restricted to the A type in Scheme I.

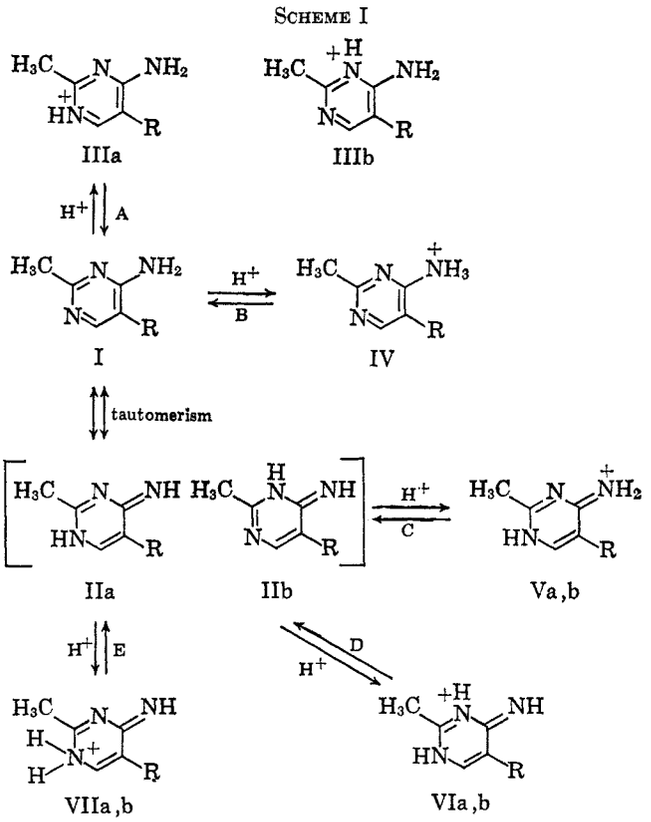
The 4-substituent of the pyrimidines studied is located at the *para* position for N-1 in the nucleus, but at the *ortho* position for N-3. Since the steric effect, so-called the *ortho* effect, is absent from the polar effect of the *para* substituent, there is a considerable difference between both polar effects of the *para* and *ortho* substituent. Accordingly, whichever nitrogen atom in the pyrimidine nucleus is an actual proton acceptor, the σ_m value can be used as a measure of the polar effect of the 5-substituent. However, if N_3 is an actual proton acceptor, the σ_p value can not be used as a measure of the polar effect of the 4-substituent on the base strength.

Jaffé[9] pointed out that the ρ value for the reaction of a series of compounds having the substituents R^1 and R^2, R^1 being varied and R^2 remaining the same for the whole series, is essentially identical with that for a series of compounds having another R^2 unless the reaction mechanism is affected by R^2. As shown in Table

(8) Brown and co-workers[7] came to the same conclusion by a ultraviolet spectrophotochemical study.

(9) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

SCHEME I



II, the ρ value for the series of the 4-aminopyrimidines is approximately identical with that for the series of the 4-dimethylamino analogs. This indicates that for 5-substituted 4-amino-2-methylpyrimidines the equilibrium A in Scheme I predominates over other protonation equilibria. Therefore, it is obvious that these 4-aminopyrimidines exist largely in the amino form in water, and that the effect of substituent on the tautomerism of these pyrimidines is negligible.

The $\Sigma\sigma$ values listed in Table I are a multiple-substituent constant for 4,5-substituents of the pyrimidines studied. The value is a total of the *meta* and the *para* substituent constants, σ_m and σ_p. The σ_m and σ_p values which have been found in the literature are used as a measure of the polar effects of 5- and 4-substituents, respectively. Figure 2 shows that a linear correlation exists between pK_a and $\Sigma\sigma$, with the exception of the 5-carboxy derivatives of 4-amino- and 4-dimethylamino-2-methylpyrimidines which will be reported in a following paper. This result supports the following hypotheses: (a) polar effect of the substituents on the base strength of the pyrimidines are proportional to the substituent constant, and are additives; and (b) the proton in the cations of these pyrimidines is bound to N-1 in the nucleus, since this nuclear nitrogen is located at the *para* position for the 4-substituent and at the *meta* position for the 5-substituent.

Moreover, the magnitude of the reaction constant deserves a comment. The value for the base strength of the pyrimidines in Table II is not significantly different from that for pyridines ($\rho = 5.714$).[2] Therefore, the ρ value is independent of the kind of nucleus[10] for the reaction of the nuclear heteroatom of heteroaromatic compounds.

(10) It was found by Imoto and co-workers[3a] that the ρ value for the reaction of a side chain is independent of the kind of nucleus.

Experimental Section

Apparatus.—The potentiometric titrations were carried out with a Yanagimoto KY-6 potentiometric titrimeter. The spectrometric measurements were carried out on a Hitachi EPU-2A spectrophotometer.

Materials.—The following pyrimidine derivatives had the melting points and properties reported in the literature and were prepared according to the cited references: 4-amino-2-methyl-, mp 204–206°;[11] 4-amino-5-carboxy-2-methyl-, mp 267° dec;[11] 4-amino-5-cyano-2-methyl-, mp 248–249°;[12] 4-amino-5-ethoxycarbonyl-2-methyl-, mp 121°;[13] and 4-amino-5-formyl-2-methyl-, mp 193–194°.[14]

4-Amino-5-carbamoyl-2-methylpyrimidine.—A mixture of 10 g of the above cyano derivative and 70 ml of Amberlite IRA-400 resin (OH type) in 500 ml of water was boiled for 1 hr and filtered. After cooling, the filtrate deposited 10 g of crystals, which were recrystallized from hot water as colorless needles, mp 265–266°.

Anal. Calcd for $C_6H_9N_4O$: C, 47.36; H, 5.30; N, 36.83. Found: C, 47.28; H, 5.10; N, 36.57.

4-Dimethylamino-2-methylpyrimidine.—In 15 ml of ethanol solution saturated with dimethylamine at 0°, 0.7 g of 4-chloro-2-methylpyrimidine[15] was heated in a sealed tube at 100° for 3 hr. The reaction mixture was evaporated completely under reduced pressure. This pyrimidine was isolated as the picrate from the oily residue in the usual way and purified by recrystallization from ethanol, mp 209–211°.

Anal. Calcd for $C_7H_{11}N_3 \cdot C_6H_3N_3O_7$: C, 42.62; H, 3.85; N, 22.94. Found: C, 42.89; H, 4.03; N, 22.83.

This picrate was converted to the free base in water by addition of Amberlite IRA-400 resin (OH type). The concentration of the base was determined by titration with HCl.

4-Dimethylamino-5-ethoxycarbonyl-2-methylpyrimidine.—In 30 ml of ethanol solution saturated with dimethylamine at 0°, 3 g of 4-chloro-5-ethoxycarbonyl-2-methylpyrimidine[13] was heated in a sealed tube at 100° for 3 hr. The reaction mixture was evaporated under reduced pressure, diluted with water, and extracted with ether. The ethereal layer was washed with water dried over Na_2SO_4, and evaporated. This ester was obtained from the brown oily residue by distillation under reduced pressure, bp 124–126° (6 mm).

Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.29; H, 7.48; N, 19.93.

4-Dimethylamino-5-carboxy-2-methylpyrimidine.—In 20 ml of 5% KOH solution, 2 g of the above ester was heated on a steam bath for 1 hr. After cooling, the reaction mixture was adjusted to pH 6 by addition of Amberlite IR-120 resin, filtered, and evaporated to dryness. Recrystallization of the residue from methanol–acetone mixed solvent gave 1.2 g of colorless crystals, mp 182–184°.

Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.19; H, 6.24; N, 23.16.

4-Dimethylamino-5-cyano-2-methylpyrimidine.—In 20 ml of ethanol solution saturated with dimethylamine at 0°, 3 g of 4-chloro-5-cyano-2-methylpyrimidine[16] was heated under reflux for 2 hr. The reaction mixture was evaporated and poured into ice-cold water. Recrystallization of the precipitate from aqueous ethanol gave 2.3 g of colorless needles, mp 132–134°.

Anal. Calcd for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.55. Found: C, 59.36; H, 6.40; N, 34.81.

4-Dimethylamino-5-carbamoyl-2-methylpyrimidine was prepared from the above cyano derivative (1 g) by the same method used for the 4-amino analog, mp 244–245°.

Anal. Calcd for $C_8H_{12}N_4O$: C, 53.32; H, 6.71; N, 31.09. Found: C, 53.37; H, 6.93; N, 31.32.

4-Acetamido-5-ethoxycarbonyl-2-methylpyrimidine.—A mixture of 1.5 g of 4-amino-5-ethoxycarbonyl-2-methylpyrimidine and 6 ml of acetic anhydride was heated at 120° for 1 hr. The reaction mixture was poured into ice-cold water, basified with K_2CO_3, and extracted with ether. The ethereal layer was washed with ice-cold water, dried over Na_2SO_4, and evaporated to dryness.

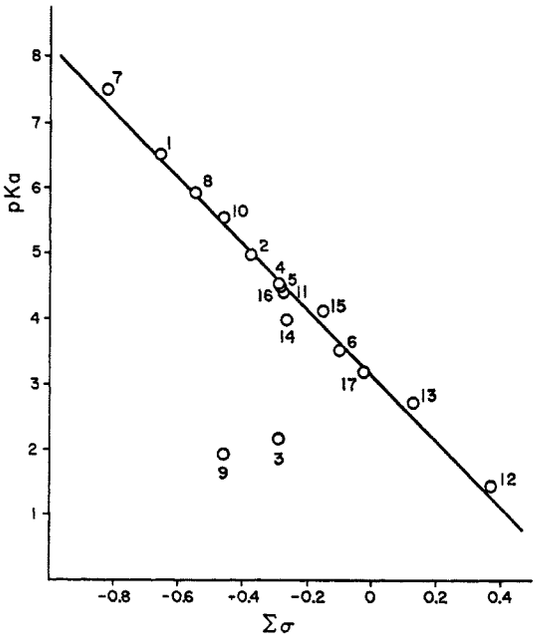


Figure 2.—Variation of pK_a with $\Sigma\sigma$ for 4,5-substituted 2-methylpyrimidines.

Recrystallization of the residue from petroleum ether (bp 40–60°) gave 1.2 g of colorless needles, mp 94–95°.

Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.83. Found: C, 53.67; H, 6.11; N, 18.53.

4-Ethoxy-5-ethoxycarbonyl-2-methylpyrimidine.—To a solution of 7 g of sodium ethoxide in 100 ml of absolute ethanol was added 3 g of 4-chloro-5-ethoxycarbonyl-2-methylpyrimidine.[13] The solution was refluxed for 1.5 hr. After neutralization by passing dry CO_2 gas and centrifugation, the resultant solution was evaporated to dryness under reduced pressure. The residue was dissolved in ice-cold water and extracted with ether. The ethereal layer was washed with water, dried over Na_2SO_4, and evaporated. Recrystallization of the residue from aqueous acetone gave 2.5 g of colorless needles, mp 52.5°.

Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 56.99; H, 6.79; N, 13.25.

4-Methoxy-2-methylpyrimidine.—To a solution of 1.4 g of sodium methoxide in 20 ml of absolute methanol was added 1.5 g of 4-chloro-2-methylpyrimidine.[15] The solution was refluxed for 7 hr. The reaction mixture was evaporated under reduced pressure, diluted with water, and extracted with ether. The ethereal layer was washed with water and evaporated. This pyrimidine was isolated as the picrate from the brown, oily residue. Recrystallization from ethanol gave 1.2 g of yellow needles, mp 159°.

Anal. Calcd for $C_5H_8N_2O \cdot C_6H_3N_3O_7$: C, 40.80; H, 3.14; N, 19.82. Found: C, 40.87; H, 3.29; N, 19.58.

For the determination of the pK_a value the free base was prepared as follows. The picrate was dissolved in NaOH solution and extracted with ether. After the ethereal layer was washed well with water, dried over Na_2SO_4, and evaporated under reduced pressure, the free base was obtained as a colorless oil.

4-Isopropoxy-2-methylpyrimidine.—In a solution of sodium isopropoxide prepared by dissolving 0.6 g of sodium in 30 ml of isopropyl alcohol, 1.5 g of 4-chloro-2-methylpyrimidine[15] was heated under reflux on a steam bath for 4 hr. The reaction mixture was treated with the same method as described in the case of the 4-methoxy analog. Recrystallization of the picrate from ethanol gave 1.1 g of yellow needles, mp 146–148°.

Anal. Calcd for $C_8H_{12}N_2O \cdot C_6H_3N_3O_7$: C, 44.10; H, 3.97; N, 18.37. Found: C, 44.13; H, 4.15; N, 18.26.

The free base was prepared by the method described in the 4-methoxy analog.

2-Methyl-4-phenoxypyrimidine.—A mixture of 1.8 g of 4-chloro-2-methylpyrimidine,[15] 5 g of potassium phenoxide, and 0.1 g of Cu powder in 15 ml of dioxane was heated in a sealed tube at 150° for 4 hr. The reaction mixture was evaporated, diluted with water, basified with K_2CO_3, and extracted with ether. The ethereal layer was washed with water and evaporated. The pyrimidine was isolated as the picrate from the

(11) T. Matsukawa, B. Ohta, and K. Shirakawa, *Yakugaku Zasshi*, **70**, 283 (1950).
(12) R. Grewe, *Z. Physiol. Chem.*, **242**, 95 (1936).
(13) A. R. Todd and F. Berger, *J. Chem. Soc.*, 364 (1937).
(14) D. Price, E. L. May, and F. D. Pickel, *J. Am. Chem. Soc.*, **62**, 2818 (1940).
(15) S. Gabriel, *Ber.*, **37**, 3638 (1904).
(16) P. Nesbitt and P. Sykes, *J. Chem. Soc.*, 3057 (1954).

residue. Recrystallization of the picrate from ethanol gave 1.2 g of yellow needles, mp 155–158°.

Anal. Calcd for $C_{11}H_{10}N_2O \cdot C_6H_3N_3O_7$: C, 49.16; H, 3.16; N, 16.86. Found: C, 49.07; H, 3.35; N, 17.10.

The free base was obtained from the picrate by the same treatment as described in the 4-methoxy analog.

4,5-Dimethoxy-2-methylpyrimidine.—To a solution of 2.4 g of sodium methoxide in 20 ml of absolute methanol was added 2.1 g of 4-chloro-5-methoxy-2-methylpyrimidine.[17] After refluxing on a steam bath for 6 hr, the reaction mixture was evaporated under reduced pressure, diluted with water, and extracted with ether. The ethereal layer was washed with water, dried over Na_2SO_4, and evaporated to dryness. Recrystallization of the residue from petroleum ether gave 1.5 g of colorless needles, mp 54°.

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.53; H, 6.63; N, 18.31.

(17) Z. Buděšinský, V. Bydžovský, J. Kopecký, A. Šváb, and J. Vavřina, *Česk. Farm.*, **10**, 241 (1961); *Chem. Abstr.*, **55**, 25973 (1961).

Acknowledgment.—The authors wish to express their deep appreciation to Dr. K. Takeda, Director of this laboratory, for his helpful advice and encouragement.

Hypophosphorous Acid, a Novel Reagent for the Reduction of Diselenides and the Selenol-Catalyzed Reduction of Disulfides[1,2]

WOLFGANG H. H. GÜNTHER

Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut

Received November 3, 1965

Aliphatic and aromatic diselenides are reduced to the corresponding selenols by treatment with hypophosphorous acid. Disulfides, sulfoxides, and aromatic azo compounds do not react with hypophosphorous acid alone, but a catalytic reduction results when small amounts of diselenides are present. The preparation of γ-selenolbutyrolactone, the first aliphatic selenolactone, is described.

The recent finding[2,3] that bis(2-trimethylammoniumethyl)diselenide diiodide[4] is smoothly reduced to the corresponding selenol by treatment with hypophosphorous acid in ethanol appeared to merit an investigation into the general applicability of this novel reduction method.

The reduction of diselenides to selenols or selenol anions has been carried out by a variety of procedures. Diphenyl diselenide can be reduced by treatment with metallic sodium in ethanol.[5] Zinc and hydrochloric acid at 40–50° have also been employed with aromatic diselenides.[6] Sodium in liquid ammonia was used to reduce dialkyl diselenides,[7] for example, to prepare methylselenol from dimethyl diselenide,[8] as well as to remove the protecting groups from benzyl alkyl monoselenides.[9] The treatment of diaryl or dibenzyl diselenides with sodium ethoxide has resulted in the formation of selenomercaptide anion, which was then utilized for further reactions without isolation.[10,11] The above alkali treatment does, however, result in poor yields owing to the concomitant formation of selenenate ion which, in turn, can be avoided, if a reducing agent such as glucose is present.[12] The latter mode of reduction was applied especially to dinitrodiaryl diselenides, which were reported to be resistant to reduction by other methods. The most convenient method, so far, appears to be the cleavage of diselenide groups by sodium borohydride[4,13] in aqueous or methanolic solution or by lithium aluminum hydride in ether[14] to form the selenols quantitatively, if oxidative losses during the work-up are avoided.

The choice of any of the above methods is determined to a large extent by the further reactions the selenol is to be subjected to and by the many desirable or undesirable side reactions which may occur. Thus, alkaline conditions are contraindicated if the selenol itself is unstable or if it contains other groups which are affected at high pH, such as the quaternary ammonium group in the preparation of cholineselenol.[3] The oxidation of selenols by atmospheric oxygen does, also, proceed most readily in alkaline solution. Use of heavy metals may be disadvantageous owing to the ease with which selenols form stable salts or complexes with the metal ion.[15] Sodium in liquid ammonia is very useful to remove protecting benzyl groups from sulfides and selenides as well as from oxygen functions. The ability to cleave a carbon–chalcogen bond, which is utilized here to great advantage, does, however, extend to the cleavage of aliphatic carbon–selenium bonds and may result in the complete removal of selenium from the desired organic residue.[16] Sodium borohydride again has the disadvantage of being used in alkaline solution. It does, also, generate hydrogen gas during the reaction and the preparation of large amounts of selenol has to be undertaken very cautiously to avoid overheating. This reagent's main advantage is the possibility of working in aqueous solution and its inertness toward many other functional groups[17] in contrast to lithium aluminum hydride, which requires nonpolar solvents and where many functional groups are reduced as well.[17]

(1) This work was supported, in part, by a grant from the U. S. Public Health Service (CA 3937).

(2) A preliminary account of this work was presented before the Medicinal Chemistry Section at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965; Abstracts, p 27-N.

(3) W. H. H. Günther and H. G. Mautner, *J. Med. Chem.*, **8**, 845 (1965).

(4) W. H. H. Günther and H. G. Mautner, *ibid.*, **7**, 229 (1964).

(5) F. Krafft and R. E. Lyons, *Ber.*, **27**, 1763 (1894).

(6) H. Rheinboldt in Houben–Weyl, "Methoden der Organischen Chemie," Georg Thieme Verlag, Stuttgart, 1955, p 961.

(7) M. L. Bird and F. Challenger, *J. Chem. Soc.*, 570 (1942).

(8) G. E. Coates, *ibid.*, 2839 (1953).

(9) E. P. Painter, *J. Am. Chem. Soc.*, **69**, 232 (1947).

(10) E. Fromm and K. Martin, *Ann.*, **401**, 185 (1913).

(11) O. Behagel and K. Hofmann, *Ber.*, **72**, 699 (1939).

(12) M. Claasz, *ibid.*, **45**, 2424 (1912).

(13) B. Sjöberg and S. Herdevall, *Acta Chem. Scand.*, **12**, 1347 (1958).

(14) S. H. Chu, W. H. H. Günther, and H. G. Mautner, *Biochem. Prepn.*, **10**, 153 (1963).

(15) A. Fredga, *Arkiv Kemi Mineral. Geol.*, **B11**, No. 44 (1934); Dissertation, University of Uppsala, 1935.

(16) W. H. H. Günther and H. G. Mautner, *J. Am. Chem. Soc.*, **87**, 2708 (1965).

(17) N. C. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p 13 ff.