Bull. Chem. Soc. Jpn., **62**, 2562—2566 (1989) [Vol. 62, No. 8

Nucleophilic Substitution Reactions of Alkyl Halides by Using New Polymer-Supported Reagents Containing Hemin

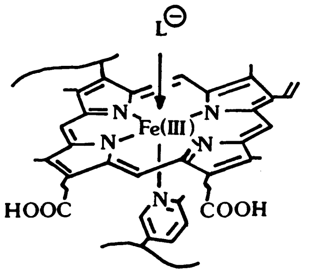
Kiyoshi Saito and Kaoru Harada*
Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305

(Received January 5, 1989)

A new polymer reagent consisting of hemin, divinylbenzene, and 2-methyl-5-vinylpyridine was synthesized by suspension copolymerization. Substitution reactions of primary, secondary, and tertiary alkyl halides with the hemin copolymer combined with cyanide, azide, and thiocyanate ions were given satisfactory yields. This reaction mechanism was revealed to be a $S_{N}i$ type on the basis of stereochemical study. The hemin copolymer was not only a polymer-supported reagent with functional capabilities, but also served to separate the product from the reaction mixture.

Ferri-protoporphyrin IX chloride (hemin) is a kind of tetrapyrrole derivative containing a large π-electron system and shows aromatic property. The axial coordination site of porphyrin is an interesting reaction field for various organic reactions. Recently, catalytic oxidation and epoxidation using metalloporphyrin complexs have revealed that the reactions take place on the coordination site of the metalloporphyrin.[1] However, studies on the reaction using ligands other than oxygen have not been reported to the best of our knowledge. Methemoglobin or ferrihemoglobin, in which the heme-ion carries an extra positive charge, has been found to have high affinity for cyanide ion.[2] We have synthesized beads shape hemin containing copolymer by suspension copolymerization[3] in order to prevent the stacking of hemin. It has been shown that the copolymer functions as a cyanide ion exchanger.[3] In this study we would like to describe the application of the hemin copolymer combined with various ligands as a polymer-supported reagent, for nucleophilic substitution in nonaqueous solvents. The use of crown ether as a phase transfer catalyst and of commercial anion-exchange resin as a polymer reagent for nucleophilic substitution in nonaqueous system has been reported.[4–7] In these systems, the mechanism of the reaction is of the S_N2 type. The nucleophilic substitution using Amberlyst A26 (**2**), was reported previously in a nonaqueous system.[5] The polymer investigated in this study is a copolymer consisting of hemin, divinylbenzene (DVB), and 2-methyl-5-vinylpyridine (MVP) (**1**). Figure 1 shows the difference in the binding of the nucleophile at the ion exchange site of **1** and **2**. In **2**, the nucleophile is combined with electrostatic interaction. On the other hand, in **1**, the chemical bonding of the nucleophile with the central iron has both electrostatic and also coordination properties.

Hemin-copolymer (1)



Amberlyst A26 (2)

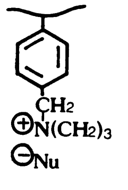


Fig. 1. The difference in the binding of the nucleophile at the ion exchange site of **1** and **2**.

Experimental

Synthesis of Hemin Copolymer (1) by Suspension Polymerization:[3] All the monomers used were as described previously.[3] The suspension polymerization was carried out with a standard apparatus for suspension polymerization.

Adsorption Experiment with Cyanide Ion: Copolymer **1** (chloride form, 0.155—0.189 g) was stirred in 50 ml $Na_2B_4O_5$-KH_2PO_4 buffer solution (pH 9; ionic strength 0.1) containing different amounts of KCN (2.14×10^{-4}—2.14×10^{-2} mol dm^{-3}). Detailed procedures of the experiments have been described previously.[3] **Azide Ion:** Copolymer **1** (chloride form, 0.155—0.189 g) was stirred for 12 h in water (50 ml) containing different amounts of NaN_3 (2.14×10^{-4}—2.14×10^{-2} mol dm^{-3}). The azide ion concentration of the supernatant was measured by the method of Labruto and Randisi.[8] **Thiocyanate Ion:** Copolymer **1** (chloride form, 0.155—0.189 g) was stirred for 12 h in water (50 ml) containing different amounts of KSCN (2.14×10^{-4}—2.14×10^{-2} mol dm^{-3}). The thiocyanate ion concentration of the supernatant was measured by the method of Kruse and Mellon.9)

Polymer-Supported Reagents (CN, N_3, SCN-Modified Hemin Copolymer): Copolymer **1** (chloride form, 10.0 g) was stirred for 12 h with potassium cyanide (7.0 g) or sodium azide (7.0 g) or potassium thiocyanate (10.0 g) in water (100 ml). The treated resin was filtered off and washed successively with water, methanol, and acetone before drying under reduced pressure at 60 °C.

To estimate the molar quantity of the nucleophile combined with the hemin copolymer, the prepared polymer-supported reagent was packed in a column (40 cm×10 mm diameter) and the nucleophile was eluted with 0.5 M NaOH.

CN, N_3, SCN-Bound Amberlyst A26:5) Amberlyst A26 (chloride form, 100 g) was stirred for 6 h with potassium cyanide (42 g) or sodium azide (42 g) or potassium thiocyanate (60 g) in water (400 ml). The resin was filtered off and washed successively with water, tetrahydrofuran, and ether before drying under reduced pressure at 40 °C.

Substitution Reactions. The typical procedure of the substitution reaction is as follows: a mixture of halide (1 mmol), **1**-supported anion or **2**-supported anion (1 mmol), and benzene (30 ml) was stirred and heated at 60 °C or 80 °C for 10 h. The resin was filtered off and washed successively with benzene (10 ml×2) and ether (10 ml×2) (the ether was used for washing to elute the substitution product completely). The chemical yields were determined by GC analysis in comparison with authentic samples. The product was confirmed by IR and ^1H NMR spectrometry.

Synthesis of Optically Active α-Bromo Acid Methyl Ester. Optically active α-bromo acids were prepared from (*R*)- or (*S*)-amino acids in the usual way as follows: (*S*)-(−)-leucine (10 g, 76 mmol) in cold 3 M H_2SO_4 (300 ml; 1M=1 mol dm^{-3}), containing potassium bromide (55 g, 6 mol equiv) was treated with sodium nitrite (15 g, 2.7 mol equiv) at 0°C for 0.5 h. The solution was kept at 0 °C for 1 h and then stirred for 1 h with ether (150 ml). The layers were separated and the aqueous solution was extracted with ether. The combined organic solution was dried ($MgSO_4$) and evaporated. After distillation of the crude product, 9.2 g (62%) of purified (*S*)-2-bromo-4-methylpentanoic acid was obtained, bp 97—98 °C (33.33 Pa); $[\alpha]_D^{20}-33.4°$ (*c* 2, methanol), lit, $[\alpha]_D^{27}-34°$ (methanol).10) Esterification of the acid with diazomethane gave (−)-methyl-(*S*)-2-bromo-4-methylpentanoate, bp 50 °C (267 Pa). All optical purities of (*R*)- or (*S*)-α-bromo acids were determined by polarimeter before esterification with diazomethane.

(*R*)-2-Bromo propanoic acid, $[\alpha]_D^{22}+27.3°$ (*c* 2, methanol), 84% e.e., lit, $[\alpha]_D^{23}+32.4\pm3.6°$ (*c* 0.49, methanol);16) (*S*)-2-bromo propanoic acid $[\alpha]_D^{22}-24.5°$ (*c* 2, methanol), 89% e.e., lit, $[\alpha]_D^{27}-27.6°$ (methanol);10) (*R*)-2-bromo-3-phenylpropanoic acid, $[\alpha]_D^{22}+10.4°$ (*c* 2, methanol), 100% e.e., lit, $[\alpha]_D^{20}+9.0°$;17) (*S*)-2-bromo-3-phenylpropanoic acid, $[\alpha]_D^{22}-10.7°$ (*c* 2, methanol), 100% e.e., lit, $[\alpha]_D^{25}-10.0°$ (*c* 2, methanol);18) (*R*)-2-bromo-4-methylpentanoic acid, $[\alpha]_D^{22}+37.8°$ (*c* 2, methanol), 99% e.e., lit, $[\alpha]_D^{22}+38.2\pm1.8°$ (*c* 2, methanol);19) (*R*)-2-bromo-3-methylbutanoic acid, $[\alpha]_D^{22}+16.1°$ (*c* 2, methanol), 100% e.e., lit, $[\alpha]_D^{25}+15.5$ (methanol);20) (*S*)-2-bromo-3-methylbutanoic acid, $[\alpha]_D^{22}-17.2°$ (*c* 2, methanol), 100% e.e., lit, $[\alpha]_D^{27}-16.8°$ (methanol).10)

Characterization of the Substituted Product. After substitution of the optically active α-bromo acid methyl ester with N_3-modified **1**, the resulting α-azido acid methyl ester was hydrogenated over 5% or 20%-Pd/C in the usual manner to form the α-amino acid methyl ester. A 5 mg sample of the α-amino acid methyl ester in 20 ml of 3 M HCl in *i*-PrOH was heated at 100 °C (30 min). The reaction mixture was evaporated under vacuum and the residue was dissolved in 20 ml of dichloromethane. The solution was cooled by using a Dry Ice–acetone bath and 4 ml of trifuluoroacetic anhydride (TFAA) was added. The solution was warmed to room temprature, and allowed to stand for 1 h. The reaction mixture was evaporated under vacuum, the residue was dissolved in dichloromethane, and the enantiomeric excess (e.e.) was determined by GC analysis using a chiral stationary phase (Chirasil-Val III).11)

ESR Spectra. The interaction between the substituted product (R-CN, R-N_3, R-SCN) and the hemin group in copolymer **1** was characterized by electron spin resonance (ESR) spectroscopy which was made at liquid nitrogen temperature with a JEOL-8 JES-FELX spectrometer.

Separation Experiment. The substitution reaction using hemin copolymer **1** was stopped at 65% yield and the reaction mixture containing **1** was packed in a column. After unreacted substrate was compleatly removed by elution with benzene, the reaction product was eluted with ether.

Results and Discussion

Adsorption Experiment. The coordination sphere around the central iron of the hemin in the copolymer was characterized by ESR spectroscopy.3) The spectrum indicated the five-coordinated high spin type of ferri-porphyrin characterized by ESR signal with $g=6$.3) On the other hand, the axial coordination number of N_3^- and SCN^- ions was close to one, as estimated from the results of adsorption experiments similar to those described previously.3) These results could indicate that the hemin copolymer **1** contains hemin in which the fifth coordination site of the iron(III) is occupied with the MVP residue, and N_3^- and SCN^- ions bind to the sixth coodination position.

Table 1. Nucleophilic Substitution of R-X with CN^-, N_3^-, or SCN^- Ions Adsorbed onto **1**a)

R-X	Reaction temp	Yield of substituted products/%		
	°C	R-CNb)	R-N_3c)	R-SCNd)
$CH_3(CH_2)_7Br$	80	78	89	87
$CH_3(CH_2)_3Br$	60	86	92	98
$CH_3CH_2CH(CH_3)Br$	60	76	83	90
$(CH_3)_3CBr$	60	70	74	83
$CH_3CH_2C(CH_3)_2Br$	60	70	73	81
$PhCH_2Br$	60	75	92	94
$PhCH(CH_3)Br$	80	78	80	86
$(Ph)_2CHBr$	80	76	80	83
$(Ph)_2C(CH_3)Br$	80	73	75	78
$(Ph)_3CBr$	80	80	80	82
Me_3Si-Cl	60	91	91	97

a) 6 h, [R-X]=[**1**-Nu]=1 mmol/30 ml benzene. b) Reaction with CN^- ion adsorbed onto **1**. c) Reaction with N_3^- ion adsorbed onto **1**. d) Reaction with SCN^- ion adsorbed onto **1**.

Table 2. Nucleophilic Substitution of R-X with CN^- Ion Adsorbed onto Commercial Anion Exchange Resins or KCN

Substrate	X	Reaction condition				Yield of nitrile	Ref.
		Reagent[a]	Solv.	Temp	Time		
				°C	h	%	
$CH_3(CH_2)_2X$	Br	a	—	80	1	70	1
$CH_3(CH_2)_3X$	Br	a	—	80	1	65	1
$CH_3CH_2CH(CH_3)X$	Cl	a	—	110	1	24	1
$(CH_3)_3CX$	Cl	a	—	110	1	0	1
	Br	KCN	DMSO			Elimination product	13
$CH_3(CH_2)_7X$	Br	b	Benzene	80	6	90	2
$PhCH_2X$	Br	a	EtOH	65	1.5	53	3
		b	Benzene	79	6	87	2

a) Abbreviations used : a, CN-bound Amberlite IRA400; b, CN-bound Amberlyst A26.

Substitution Reactions. The results are summarized in Table 1. The yields of the resulting nitrile, azide, or thiocyanate from halides are high, and byproducts were not detected in the reaction mixture, even though the results described here were obtained by using equimolar reagents. Commercial anion-exchange resins have also been used as the polymer-reagent in substitution reactions involving cyanide ion.[4-6] However these commercial resins were not very active in the substitution reaction. Secondary halides gave the corresponding nitriles in low yields, and tertiary halides did not give any substitution products (Table 2). Previously, trimethylacetnitrile has been prepared by dehydration of trimethylacetamide[12] or by addition reaction of HCN to isobutene.[13] The substitution reaction of *t*-butyl bromide with KCN in DMSO did not give the corresponding nitrile but yielded the elimination product (Table 2).[14]

After the substitution reaction, it was found that most of the products were adsorbed onto the hemin site in the resin. The adsorbed products could easily be desorbed with ether or hexane.

The polymer reagent described in this paper is much more effective than the commercial anion-exchange resins, probably because the cyanide ion is adsorbed at the hemin site in **1** with ionic as well as with coordination bond. Taking this point into account, the substitution reaction of cinnamyl bromide with thiocyanate ion was investigated (Table 3). Harrison and Hodge have described this reaction using **2**-supported thiocyanate[5] (Table 3). They reported that the initial product of the reaction between **2**-supported thiocyanate and cinnamyl bromide was cinnamyl thiocyanate, but after prolonged reaction time the product rearranged to isothiocyanate.[5] In our reaction, however the only product obtained by the substitution reaction was cinnamyl thiocyanate under the same reaction conditions as Ref. 5). Therefore, the rearrangement of the initial product was prevented by the coordination of the product on the hemin site.

Table 3. Nucleophilic Substitution of Cinnamyl Bromide[a] with SCN^- Ion Adsorbed onto **1** or **2**

Substrate	Product group	Yield of product/%			
		1		**2**[2]	
		Benzene	Toluene	Benzene	Toluene
PhCH=CHBr	-SCN	99	98	67	11
	-NCS	0	0	31	82

a) 80 °C, 6 h.

ESR Spectra. From the results described above, it can be assumed that some interaction exist between the product and the hemin residue under the reaction conditions. This interaction could be confirmed by ESR spectrometry (Fig. 2). Figure 2 shows the change of spectral pattern of butyl thiocyanate with **1**. In Fig. 2, (a) and (b) were measured before and after adsorption of the thiocyanate using a 1 : 2 mixture of the thiocyanate and benzene, and these are in accord with those of high- and low-spin Fe(III)-porphyrins, respectively. Spectrum (c) was obtained after desorp-

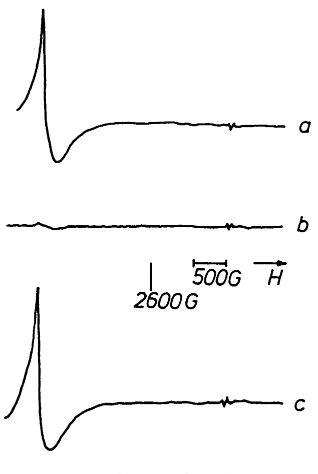
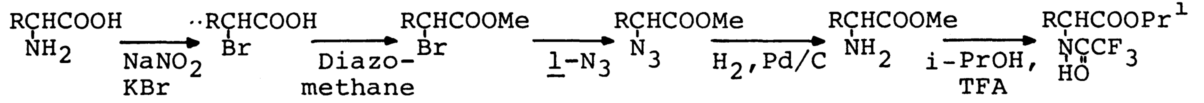


Fig. 2. ESR spectra of **1** at liquid nitrogen temperature. a, **1**; b, after adsorption of the thiocyanate for a 1 : 2 mixture of butyl thiocyanate and benzene; c, after desorption of the thiocyanate with hexane.



$$\underset{NH_2}{RCHCOOH} \xrightarrow[NaNO_2\ KBr]{} \underset{Br}{RCHCOOH} \xrightarrow[Diazo\text{-}\ methane]{} \underset{Br}{RCHCOOMe} \xrightarrow[\underline{1}\text{-}N_3]{} \underset{N_3}{RCHCOOMe} \xrightarrow[H_2,Pd/C]{} \underset{NH_2}{RCHCOOMe} \xrightarrow[i\text{-}PrOH,\ TFA]{} \underset{\underset{H\ \ O}{NCCF_3}}{RCHCOOPr^i}$$

Scheme 1.

Table 4. Nucleophilic Substitution of Optically Active α-Bromo Acid Methyl Ester [R-C*H(Br)COOMe] with N_3^- Ion Adsorbed onto **1**[a]

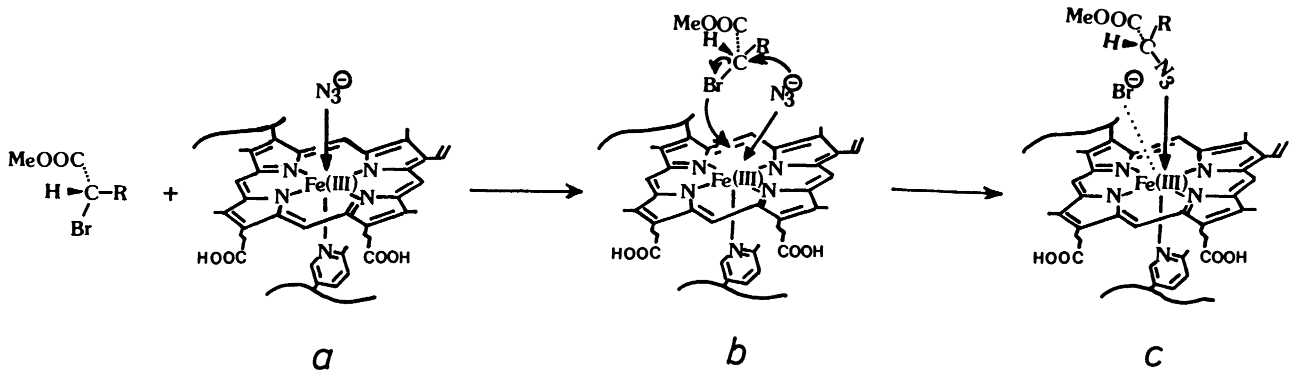
R		Reagent	O.P. [b] %	C.Y. [c] %	e.e. [d]	%	e.e. /O.P. %	Ref.
CH_3-	(*R*)	**1**-N_3^-	84	98	(*R*)	74	88	—
	(*S*)	**1**-N_3^-	89	96	(*S*)	80	90	—
$PhCH_2$-	(*R*)	**1**-N_3^-	100	93	(*R*)	97	97	—
	(*S*)	**1**-N_3^-	100	95	(*S*)	91	91	—
$(CH_3)_2CHCH_2$-	(*R*)	**1**-N_3^-	99	97	(*R*)	96	97	—
		2-N_3^-	99	10	(*S*)	80	—	—
	(*S*)	**1**-N_3^-	98	95	(*S*)	91	93	—
		2-N_3^-	100	13	(*R*)	76	—	—
		NaN_3[e]	76	38	(*R*)	79	—	15
$(CH_3)_2CH$-	(*R*)	**1**-N_3^-	100	98	(*R*)	92	92	—
	(*S*)	**1**-N_3^-	100	98	(*S*)	98	98	—

a) 6 h, 60 °C, [RCHBrCOOMe]=[N_3^-]=1 mmol/30 ml benzene. b) Optical purity of α-bromo acid. c) Chemical yield of α-azido acid methyl ester. d) Enantiomeric excess of amino acid was determined by GC analysis e) 22 h, 60 °C, presence of 18-crown-6.

tion of the thiocyanate with hexane, and the pattern agrees with that of high-spin as it was before. The same spectral changes were observed in all of the substitution products. These results indicate that the interaction of the substitution product to the hemin site is coordination bond.

Reaction Mechanism. Taking into account the results mentioned above, it could be contemplated that these reactions proceed in the vicinity of the sixth coordination site of hemin residue in **1**. And the hemin site in the polymer reagent could not only be an ion exchange site, but also an excellent reaction field in the nucleophilic substitution. In order to further investigate this point, we have carried out stereochemical studies under the same conditions in which various optically active α-bromo acid methyl esters were used. The chemical pathway from the preparation of the substrate to the final product is shown in Scheme 1. Table 4 shows the optical purity (O.P.) of the α-bromo acid, the chemical yield (C.Y.) of α-azido acid methyl ester, the enantiomeric excess (e.e.) of the derivatized amino acid, and real retention of configuration in the substitution reaction (e.e./O.P.). As is evident from Table 4, this substitution reaction proceeded almost quantitatively, and the results of the substitution reaction agreed with these of the reaction proceed with S_Ni mechanism, with e.e./O.P. of approximately 100%.[21] In contrast with our results, the yields of the substitution products using azide bound **2**, and NaN_3 in the presence of crown ethers[13] (Table 4) were both low and the configurations of the products were inverted under the same conditions we used.

The interaction between substitution product, α-azido acid methyl ester, and the hemin residue in copolymer **1** was confirmed by ESR spectrometry.



Scheme 2. A possible reaction pathway of the nucleophilic substitution of optically active α-bromo acid methyl ester with N_3^- ion combined with **1** in benzene at 60 °C.

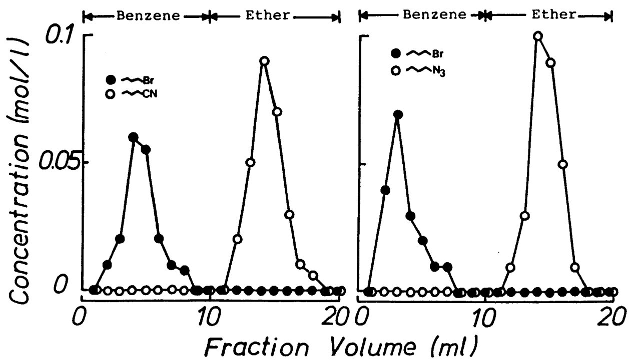


Fig. 3. Column separations of substitution reaction mixtures with **1**.

The same spectral changes were observed as shown in Fig. 2.

The mechanism of nucleophilic substitution reaction in this study could be explained as shown in Scheme 2. The nucleophile is adsorbed onto 6th coodination site of hemin in resin **1** on the basis of the coordination number of CN^-, N_3^-, and SCN^- (n=1)[3] and ESR spectra[3] (Scheme 2, *a*). It can be concluded from the results of ESR spectroscopic analysis (Fig. 2) (Scheme 2, *c*), that most of the reaction products are coordinated to the hemin site after substitution reaction. Taking into consideration the facts that (i) the substituted products were obtained from tertiary alkyl bromide in benzene; (ii) cinnamyl thiocyanate was produced in high yield; (iii) the reactions using optically active substrates proceeded with complete retention of configuration; it could be interpreted that the reaction is a $S_{N}i$ type substitution reaction (Scheme 2, *b*).

Column Separation. Copolymer **1** is not only a polymer-supported reagent with functional capability, but also serves to separate the product from the reaction mixture. The products were coordinated to hemin sites in the reaction solvent and could be desorbed easily with hexane or ether. Therefore, the separation characteristics of **1** were further investigated by using the column. The substitution reaction was stopped at 65% yield and the reaction mixture adsorbed in **1** was packed in a column. Figure 4 shows a typical column separation of the substrate (●) and the reaction product (○). When the reaction mixture was packed and eluted through a column with benzene (●), only the substrate(1-bromobutane) was in the eluent. The adsorbed reaction product (valeronitrile or butyl azide) was eluted almost completely with ether (recovery ca. 99 %).

References

1) J. T. Groves and T. E. Nemo, *J. Am. Chem. Soc.*, **105**, 5786 (1983).

2) J. M. Rifkind, *Inorg. Biochem.*, **2**, 832 (1973).

3) E. Kokufuta and K. Saito, *J. Appl. Polym. Sci.*, **34**, 517 (1987).

4) N. Urata, *Nippon Kagaku Kaishi*, **83**, 1105 (1962).

5) C. R. Harrison and P. Hodge, *Synthesis*, **1980**, 299.

6) M. Gordon and C. E. Griffin, *Chem. Ind.*, **1962**, 1019.

7) F. Manescalchi, M. Orena, and D. Savoia, *Synthesis*, **1979**, 445.

8) G. Labruto and D. Randisi, *Ann. Chem. Applic.*, **22**, 319 (1932).

9) J. M. Kruse and M. G. Mellon, *Anal. Chem.*, **25**, 446 (1953).

10) W. Gaffield and W. G. Galetto, *Tetrahedron*, **27**, 915 (1971).

11) H. Frank, G. J. Nicolson, and E. Bayer, *J. Chromatogr.*, **146**, 197 (1978).

12) W. Lehnert, *Tetrahedron Lett.*, **1971**, 1501.

13) B. S. Hendrik, *Neth. Appl.*, **69**, 495 (1971).

14) L. Friedman and H. Shechter, *J. Org. Chem.*, **25**, 877 (1960).

15) Y. Nakajima, *Tetrahedron Lett.*, **1978**, 3107.

16) H. Hashimoto and H. Simon, *Angew. Chem.*, **87**, 111 (1975).

17) E. Fischer and W. Schoeller, *Ann. Chem.*, **357**, 1 (1907).

18) A. F. Spatola and A. L. Bettag, *J. Org. Chem.*, **46**, 2393 (1981).

19) J. A. Yankeelov, Jr., K. F. Fok, and D. J. Carothers, *J. Org. Chem.*, **43**, 1623 (1978).

20) R. J. Anderson, K. G. Adams, and C. A. Henrick, *J. Agric. Food Chem.* **33**, 508 (1985).

21) P. A. Levene and A. Rothen, *J. Biol. Chem.*, **127**, 237 (1939).