9. Yu. S. Shabarov, N. I. Vasil'ev, N. K. Mamaeva, and R. Ya. Levina, Dokl. Akad. Nauk SSSR, 135, 879 (1960).
10. W. G. Overend and L. F. Wiggins, J. Chem. Soc., No. 1, 239 (1947).
11. Sh. Fel'deak, A. S. Puadzhyunas, and D. A. Daugirdene, Khim.-Farm. Zh., No. 1, 5 (1969).

PYRIMIDINES.

71.* REARRANGEMENTS OF 2,2',4-TRIMETHOXY-6'-PHENYL-4',5-DIPYRIMIDINYL TO N-METHYL OXO DERIVATIVES

I. I. Naumenko, M. A. Mikhaleva, and V. P. Mamaev

UDC 547.855.1:542.952.1

A trimethoxy derivative with three nonequivalent methoxy groups was obtained from 2,2',4-trichloro-6'-phenyl-4',5-dipyrimidinyl. Rearrangement of 2,2',4-trimethoxy-6'-phenyl-4',5-dipyrimidinyl under Hilbert–Johnson conditions and thermal rearrangement with and without a catalyst make it possible to obtain 2',4-dimethoxy-1-methyl-2-oxo- and 2'-methoxy-1,3-dimethyl-2,4-dioxodipyrimidinyls and both tri-N-methyl isomers, viz., the 1,1',3- and 1,3,3'-trimethyl derivatives. The possibility of obtaining N-methyl derivatives of trioxodipyrimidinyl by methylation under various conditions was also examined.

We have previously reported the synthesis of 2,2',4-trichloro-6'-phenyl-4',5-dipyrimidinyl (I) and the sequence of nucleophilic substitution of the chlorine atoms in the compound by an amino group [1]. Continuing our study of the unsymmetrical 4',5-dipyrimidinyl system we carried out the replacement of the chlorine atoms by methoxy groups with the aim of subsequent rearrangements of the trimethoxy derivative to the isomeric N-methyl oxo derivatives of 4',5-dipyrimidinyl. It is known that the N-alkyl oxo derivatives of pyrimidine, both in the uracil series [2] and in the case of 4,6-diaryl-substituted pyrimidines [3] display physiological activity.

The chlorine atoms in dipyrimidinyl I were readily replaced by methoxy groups when it was refluxed with a solution of sodium methoxide in methanol. The resulting 2,2',4-trimethoxy-6'-phenyl-4',5-dipyrimidinyl (II) contains three nonequivalent methoxy groups.

The rearrangements of alkoxy derivatives of the pyrimidine series to N-methyl oxo derivatives have been described in the literature. Most study has been devoted to the rearrangements of the 2,4-dialkoxy derivatives by reaction with alkyl halides (under the conditions of the Hilbert–Johnson reaction) [2] and to thermal rearrangement in the presence of amines [4, 5] or without the use of catalysts [6] for monoalkoxypyrimidines. Known examples of rearrangements of methoxydipyrimidinyls have been described only for cases with 2,4-oriented alkoxy groups in pyrimidine fragments. 2,2',4,4'-Tetramethoxy-5,5'- [7] and 2,2',4,4'-tetramethoxy-4,5'-dipyrimidinyl [8] undergo rearrangement thermally, without the addition of a catalyst, togive products of complete rearrangement, whereas in the case of a symmetrical dipyrimidinyl [7] Chang and co-workers assume that an N,N'-dimethyl methoxy derivative is formed when it is heated under Hilbert–Johnson conditions, although the PMR spectra presented in [7] indicate, in our opinion, the formation of an N,N'N''-trimethyl monomethoxy derivative of 5,5'-dipyrimidinyl. It is known that N–CH_3 and OCH_3 groups in pyrimidines can be easily distinguished from their PMR spectra — the position of the signal of the methoxy group differs from the signal of the N-methyl grouping by ∿0.5 ppm [4, 9, 10].

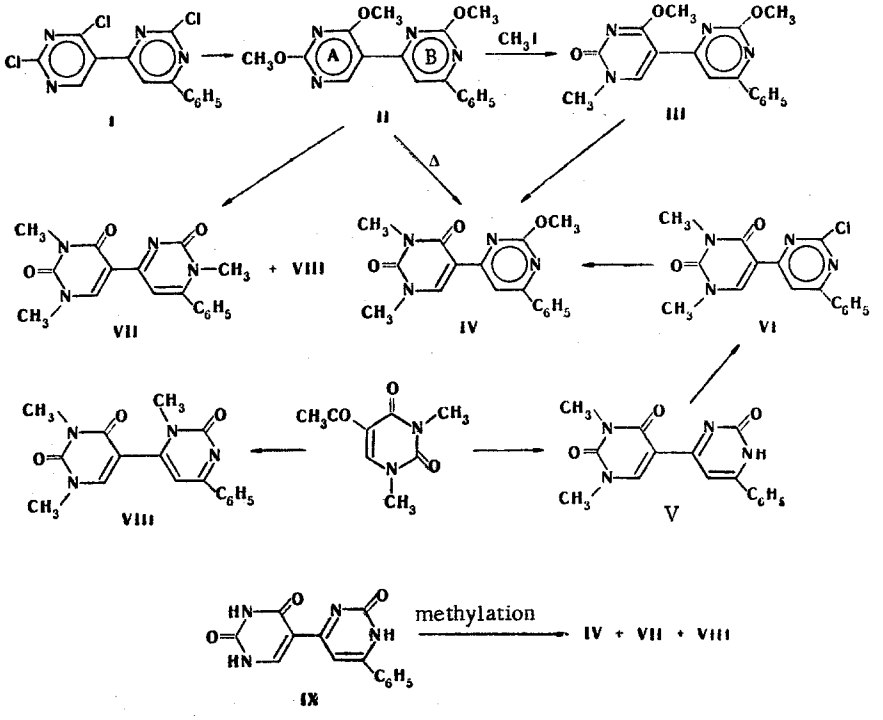
*See [1] for communication 70.

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 398-403, March, 1980. Original article submitted July 24, 1979.

0009-3122/80/1603-0303$07.50

A new compound that is isomeric with respect to the starting compound was obtained by refluxing dipyrimidinyl II with methyl iodide. The PMR spectrum of this compound (Table 1) contained signals that attest to the fact that only one methoxy group undergoes rearrangement under Hilbert–Johnson conditions. It follows from the data in [2] that rearrangement of 2-monoalkoxypyrimidines under Hilbert–Johnson conditions probably does not occur, whereas the group in the 2 position primarily undergoes rearrangement in the case of 2,4-dialkoxy derivatives. We therefore concluded that the 2-OCH_3 group of the A ring undergoes rearrangement in trimethoxydipyrimidinyl II, which contains 2,4-dimethoxy- and monomethoxy-substituted pyrimidine rings (A and B, respectively) and that the product has the 2',4-dimethoxy-2-oxo-1-methyl-6'-phenyl-1,2-dihydro-4',5-dipyrimidinyl structure (III).

Further rearrangement of III was carried out thermally, since under Hilbert–Johnson conditions this product remained virtually unchanged – an increase in the refluxing time in solution in CH_3I led to the development of only traces of other products [according to the results of thin-layer chromatography (TLC)]. Heating dipyrimidinyl III at 235-240°C led rapidly to the formation in high yield of another isomeric product (IV), which, according to the PMR data, contains one OCH_3 group. Data that indicate that the thermal rearrangement of most 2-alkoxypyrimidines proceeds slowly in the absence of catalysts [5] made it possible to assume that the product has the 2'-methoxy-2,4-dioxo-1,3-dimethyl-6'-phenyl-1,2,3,4-tetrahydro-4',5-dipyrimidinyl structure. To confirm this assumption we realized the alternative synthesis of IV from 1,3-dimethyl-5-acetyluracil via a previously developed scheme [11] through trioxo derivative V and chlorodipyrimidinyl VI. The compounds obtained were identical.



Compound IV can also be obtained in one step from trimethoxydipyrimidinyl II by thermal rearrangement with an increase in the heating time.

It was not possible to predict the direction of the rearrangement (at 1'-N or 3'-N) of the remaining 2'-methoxy group, since the problem of the rearrangements of 2-alkoxy-4,6-diarylpyrimidine with nonequivalent substituents in the 4 and 6 positions has not been studied in the literature.

In contrast to the data in [4, 5], heating 2'-methoxydipyrimidinyl IV without a catalyst at 235-240°C for several hours, as well as in triethylamine under the same conditions or at 180°C for 24 h, gave a mixture, from which we isolated only up to 50% of the starting dipyrimidinyl; N,N',N''-trimethyl derivatives were not found.

It was recently proposed that p-toluenesulfonic acid or its derivatives be used as the catalyst for rearrangements of 2,4-dialkoxypyrimidines [12]. We carried out the rearrangement of dipyrimidinyl II in the presence of p-toluenesulfonic acid under various

TABLE 1. PMR Spectra of Dipyrimidinyls II-IV and VI-VIII

Compound	Solvent	Signals of the CH_3 groups	6-H	5′-H	Intensity ratios
II	$CDCl_3$	3,99; 4,02; 4,08	9,20	—[a]	3 : 3 : 3 : 1
III	$CDCl_3$	3,53; 4,07	8,77[b]	—[a]	3 : 6 : 1
IV	$CDCl_3$	3,37; 3,47; 4,05	8,62[b]	7,22[b]	3 : 3 : 3
VI	d_7-DMF	3,30; 3,62	9,00[b]	—[a]	3 : 3
VII	$CDCl_3$	3,29; 3,39; 3,47	8,79	7,89	3 : 3 : 3 : 1 : 1
VIII	d_7-DMF	3,18; 3,33; 3,40	8,10	6,97	3 : 3 : 3 : 1 : 1

[a]Appears together with o-H_{arom} at 7.9-8.3 ppm. [b]The intensity is too high.

TABLE 2. Dipyrimidinyls II-VIII

Compound	mp, °C	R_f in systems			UV spectra, λ_{max}, nm (log ε)	M	Found, %			Empirical formula	Calc., %			Yield, %
		A	B	C			C	H	N		C	H	N	
II	130—131[a]	0,66	—	0,81	213 (4,11), 265 (4,32), 320 (4,36)	324	63,0	4,7	17,4	$C_{17}H_{16}N_4O_3$	63,0	5,0	17,3	90
III	220—223	0,32	0,36	0,69	206 (4,53), 256 (4,41), 324 (4,44)	—[b]	63,3	5,0	—	$C_{17}H_{16}N_4O_3$	63,0	5,0	17,3	78
IV	257—259	0,57	0,61	0,77	207 (4,65), 256 (4,53), 330 (4,65)	324	62,8	5,1	17,2	$C_{17}H_{16}N_4O_3$	63,0	5,0	17,3	80[c]
V	349—350	0,05	—	0,30		310	62,1	4,6	18,0	$C_{16}H_{14}N_4O_3$	62,0	4,5	18,1	87
VI	262—263	0,69	—	0,81	206 (4,39), 259 (4,36), 330 (4,41)	328	58,4	4,1	17,3	$C_{16}H_{13}ClN_4O_2$	58,5	4,0	17,0	92
VII	269—271	0,17	0,20	0,49	207 (4,53), 256 (4,39), 335 (4,39)	324	62,4	5,2	17,2	$C_{17}H_{16}N_4O_3$	63,0	5,0	17,3	26[c]
VIII	291—292	0,05	0,07	0,34	205 (4,33), 277 (4,25), 341 (4,08)	324	62,3	5,1	17,1	$C_{17}H_{16}N_4O_3$	63,0	5,0	17,3	78[d]

[a]From methanol; the remaining compounds were recrystallized from alcohol. [b]Found: M 324.1259; calculated empirical formula $C_{17}H_{16}N_4O_3$. [c]By rearrangement of dipyrimidinyl II. [d]From 1,3-dimethyl-5-acetyluracil.

conditions and found that primarily the 2-methoxy group undergoes rearrangement. Thus 60% of dipyrimidinyl III was isolated from the reaction mixture after 30 min at 180°C, while dipyrimidinyl IV was formed in only trace amounts. Lowering the temperature to 155-165°C in order to reduce resinification of the reaction mixture and increasing the heating time to 2 h led primarily to the formation of a mixture of III and IV. Rather severe conditions, viz., heating at 210°C for 5.5 h, were necessary for complete rearrangement of dipyrimidinyl II; we were able to isolate isomeric N,N',N''-trimethyl derivatives VII and VIII in low yield. According to the results of TLC dipyrimidinyl III was not present in the reaction mixture, while IV was present in small amounts.

To prove the structures of products VII and VIII we carried out the alternative synthesis of one of them by the method developed for the synthesis of the 4,5'-dipyrimidinyl system [11]. The reaction of 1,3-dimethyl-5-acetyluracil and N,N-benzalbis(N'-methylurea) [13] yielded 2,2',4-trioxo-1,3,3'-trimethyl-6'-phenyl-1,2,2',3,3',4-hexahydro-4',5-dipyrimidinyl, which was found to be identical to VIII. Compound VII is consequently the 1,1',3-trimethyl derivative.

To obtain the N-methyl derivatives we used, in addition to rearrangements of the methoxy derivatives, methylation of 2,2',4-trioxo-6'-phenyl-1,1',2,2',3,4-hexahydro-4',5-dipyrimidinyl (IX) [11], which reduces the stepwise character of the process substantially.

Of the numerous methods for N alkylation of oxopyrimidines [14] we selected a method that, according to the data of the authors, gives high yields of only the N-methyl products [15]. As a result of the reaction of trioxodipyrimidinyl IX with CH_3I in dimethyl sulfoxide (DMSO) in the presence of sodium methoxide, we obtained a three-component mixture, from which we isolated three individual compounds that are identical to products IV, VII, and VIII in a ratio of 3.2:2.8:1. In other words, the use of the method in [15] in our case led to the formation of N-methyl and O-methyl derivatives in approximately equal ratios; O alkylation occurs only in the B ring.

To increase the yield of the N,N',N''-trimethyl derivatives we checked the possibility of using other alkylating agents. Compounds IV, VII, and VIII were not obtained (according to TLC) when dipyrimidinyl IX was heated with trimethyl phosphate [16] at 210°C for 2.5 h.

Methylation of IX with dimethyl sulfate, as in the case of CH_3I, led to the formation of a mixture of IV, VII, and VIII; however, the overall yield of the N,N',N''-trimethyl derivatives considerably exceeded the yield of the O-methyl derivative (the ratio was ∿5:1). However, the ratio of the products of methylation at 1'-N and 3'-N (selectivity of the reaction) decreased to ∿2:1 (VII and VIII, respectively).

Thus, the rearrangement of trimethoxydipyrimidinyl II under Hilbert–Johnson conditions and thermal rearrangement with and without a catalyst make it possible to obtain selectively the N-monomethyl derivative, the N,N'-dimethyl derivative, and both N,N',N''-trimethyl derivatives. However, the yields of the latter are low because of the extreme difficulty with which the methoxy group in the 2' position migrates.

The characteristics of II-VIII are presented in Table 2. According to the data obtained in the Scientific-Research Institute BIKhS (Kupavna), II, IV, and VIII did not display antiphlogistic, antipyretic, or analgesic activity.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in alcohol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Varian A56/60A spectrometer with hexamethyldisiloxane as the internal standard. The molecular weights were determined with an MS-902 high-resolution mass spectrometer with a system for direct introduction at 120-150°C. Preparative TLC was carried out on Silufol UV-254 and KSK silica gel plates in chloroform–alcohol solvent systems [30:1 (A), 25:1 (B), and 10:1 (C)]. The R_f values are presented for systems with the use of purified chloroform [17].

2,2',4-Trimethoxy-6'-phenyl-4',5-dipyrimidinyl (II). A 2-g (6.0 mmole) sample of dipyrimidinyl I was added to a solution of sodium methoxide obtained from 1.2 g (52.2 mmole) of sodium and 100 ml of methanol, and the mixture was refluxed for 2 h. The solution was cooled and evaporated, and the residue was washed repeatedly with water and dried to give 1.73 g of trimethoxydipyrimidinyl II. IR spectrum: 1020, 1035 cm^{-1} (C–O–C).

2',4-Dimethoxy-2-oxo-1-methyl-6'-phenyl-1,2-dihydro-4',5-dipyrimidinyl (III). A mixture of 136 mg (0.42 mmole) of dipyrimidinyl II and 4.5 mg of dry methyl iodide was refluxed for 6 h, after which it was cooled, and the solution was evaporated. The brown residue was refluxed with 3 ml of alcohol, the mixture was cooled in a refrigerator, and the white precipitate of III was removed by filtration to give 106 mg of product. IR spectrum: 1027, 1263 (C–O–C); 1640, 1670 cm^{-1} (C=O).

2'-Methoxy-2,4-dioxo-1,3-dimethyl-6'-phenyl-1,2,3,4-tetrahydro-4',5-dipyrimidinyl (IV). A) A 0.4-g (1.23 mmole) sample of II was placed in a wide test tube and heated at 235-240°C for 1.5 h. The brown melt was dissolved in $CHCl_3$ and separated by preparative TLC on silica gel in system B. Workup of the zone with R_f 0.5-0.7 yielded 0.32 g of colorless IV. IR spectrum: 1660, 1710 cm^{-1} (C=O).

B) A 0.12-g (0.37 mmole) sample of III was heated at 235-240°C for 30 min. Subsequent workup of the melt was carried out as in method A. The yield of IV was 95 mg (78%).

C) A 0.2-g (0.61 mmole) sample of dipyrimidinyl VI was added to a solution of sodium methoxide obtained from 0.03 g (1.3 mmole) of sodium and 10 ml of methanol, and the mixture was refluxed for 6 h. The white precipitate that formed after the mixture was allowed to stand in a refrigerator overnight was removed by filtration, washed repeatedly with water, and dried. The yield of IV was 0.16 g (81%).

1,3-Dimethyl-5-acetyluracil. A suspension of 2 g of dry sodium methoxide in 50 ml of absolute DMSO was added to a solution of 0.5 g (3.34 mmole) of 5-acetyluracil in 75 ml of absolute DMSO, 50 ml of freshly distilled methyl iodide was added dropwise, and the mixture was heated on a water bath at 70°C for 5 min. It was then cooled rapidly and poured into water, and the aqueous mixture was extracted with chloroform (six 40-ml portions). The chloroform solution was washed with water, dried with $MgSO_4$, and evaporated. The white residue was washed with ether and sublimed (170°C/1.5 mm) to give 0.35 g (58%) of 1,3-dimethyl-5-acetyluracil with mp 182-182.5°C (mp 175°C [18]).

2,2',4-Trioxo-1,3-dimethyl-6'-phenyl-1,1'2,2',3,4-hexahydro-4',5-dipyrimidinyl (V). A 236-mg (1.3 mmole) sample of 1,3-dimethyl-5-acetyluracil and 541 mg (2.6 mmole) of benzalbisurea were added to a solution of 98 mg (2.7 mmole) of dry HCl in 4.25 ml of absolute n-butanol, and the mixture was refluxed for 7 h. It was then allowed to stand in a refrigerator overnight, and the resulting yellow precipitate was removed by filtration and washed with 10% $NaHCO_3$ solution, water, alcohol, and ether. The yield was 350 mg (87%).

2'-Chloro-2,4-dioxo-1,3-dimethyl-6'-phenyl-1,2,3,4-tetrahydro-4',5-dipyrimidinyl (VI). Two drops of water were added to a mixture of 0.35 g (1.1 mmole) of dipyrimidinyl V, 3.5 ml of freshly distilled $POCl_3$, and 0.35 ml of dimethylaniline, and the mixture was refluxed for 4 h. It was then cooled to 20°C, and the resulting light-pink solution was poured over ice. The white precipitate was removed by filtration and washed thoroughly with water. The yield was 0.34 g.

2,2',4-Trioxo-1,3,3'-trimethyl-6'-phenyl-1,2,2',3,3',4-hexahydro-4',5-dipyrimidinyl (VIII). A 0.56 g (3.1 mmole) sample of 1,3-dimethyl-5-acetyluracil and 1.41 g (6.2 mmole) of benzalbis(N'-methylurea) were added to a solution of 0.24 g (6.6 mmole) of dry HCl in 10 ml of absolute n-butanol, and the mixture was refluxed for 8.5 h. The white crystals that formed after the mixture was allowed to stand in a refrigerator for several days were removed by filtration and washed with ether. The yield was 0.78 g. IR spectrum: 1670, 1715 cm^{-1} (C=O).

Thermal Rearrangement of 2,2',4-Trimethoxy-6'-phenyl-4',5-dipyrimidinyl (II). A mixture of 0.2 g (0.617 mmole) of dipyrimidinyl II and 0.02 g of p-toluenesulfonic acid was heated at 210°C in an argon atmosphere for 5.5 min. The resulting black melt was separated preparatively on silica gel in system B; workup of the zone with $R_f \sim 0.2$ yielded a brown product. Washing of the latter with ether gave 0.024 g (12%) of a compound with mp 286-290°C (from alcohol), which was identical to dipyrimidinyl VIII with respect to its IR spectrum. Similarly, workup of the zone with R_f 0.40 yielded 0.052 g (26%) of isomeric (with respect to VIII) dipyrimidinyl VII with mp 267-268°C (from alcohol).

Methylation of 2,2',4-Trioxo-6'-phenyl-1,1',2,2',3,4-hexahydro-4',5-dipyrimidinyl (IX). A) A suspension of 2.4 g of dry sodium methoxide in 50 ml of absolute DMSO was added to a solution of 0.46 g (1.6 mmole) of trioxodipyrimidinyl IX in 50 ml of absolute DMSO, after which 50 ml of freshly distilled methyl iodide was added dropwise, and the solution was

heated at 70°C for 5 min. It was then cooled rapidly and poured into water, and the aqueous mixture was extracted with chloroform (five 50-ml portions). The chloroform solution was washed with water, dried over $CaCl_2$, evaporated to the minimal volume, and applied to a column filled with silica gel. The product was chromatographed in system B to give 132 mg (25%) of IV, 113 mg (22%) of VII, and 43 mg (8%) of VIII.

B) A suspension of 1 g (3.55 mmole) of oxopyrimidine IX in a solution of 0.5 g (12.5 mmole) of NaOH in 15 ml of water was stirred until a homogeneous gelatinous mass formed, after which 1.2 ml (10.7 mmole) of distilled dimethyl sulfate was added dropwise, and the mixture was stirred for 4 h. The white precipitate was removed by filtration, washed thoroughly with water, and dried to give 0.74 g of a mixture, which was separated by preparative TLC on silica gel in system B. Workup of the zones with R_f 0.1, 0.2-0.3, and 0.5-0.7 gave, respectively, 0.15 g (13%) of pyrimidine VIII, 0.29 g (25%) of VII, and 0.091 g (8%) of dipyrimidinyl IV.

LITERATURE CITED

1. M. A. Mikhaleva, I. I. Naumenko, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 6, 821 (1979).
2. J. Pliml and M. Prystas, Advances in Heterocyclic Chemistry, Vol. 8, Academic Press, New York–London (1967), p. 115.
3. G. E. Hardtman and F. G. Kathawala, Swiss Patent No. 539053 (1973); Chem. Abstr., 79, 115608 (1973).
4. D. J. Brown and T.-C. Lee, Austr. J. Chem., 21, 243 (1968).
5. D. J. Brown and T.-C. Lee, J. Chem. Soc., C, No. 1, 214 (1970).
6. D. J. Brown, The Pyrimidines, Suppl. I, Wiley Interscience, New York–London (1970), p. 276.
7. S.-H. Chang, J. Y. Koo, and Y. H. Kim, Korean Chem. Soc., 18, 210 (1974).
8. L. Strekowski, Pol. J. Chem., 52, 283 (1978).
9. The Sadtler Standard Spectra. NMR Spectra, Sadtler Research Laboratory, No. 5484.
10. The Sadtler Standard Spectra. NMR Spectra, Sadtler Research Laboratory, No. 12800.
11. M. A. Mikhaleva, V. V. Gulevich, I. I. Naumenko, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 5, 678 (1979).
12. T. Kato, N. Oda, and I. Ito, Chem. Pharm. Bull., 25, 215 (1977).
13. H. Schiff, Ann., 291, 367 (1896).
14. D. J. Brown, The Pyrimidines, Suppl. I, Wiley Interscience, New York–London (1970), p. 269.
15. W. F. Bryant and P. D. Klein, Anal. Biochem., 65, 73 (1975).
16. K. Yamauchi and M. Kinoshita, J. Chem. Soc., Perkin Trans. I, No. 4, 391 (1973).
17. A. Gordon and R. Ford, Chemist's Companion: A Handbook of Practical Data, Techniques, and References, Wiley (1973).
18. S. Senda, H. Kosaku, and J. Notani, Chem. Pharm. Bull., 20, 1380 (1972).