ANALOGS OF PURINE NUCLEOSIDES.

3.* ALKOXYALKYLATION OF HYPOXANTHINE BY THE SILYL METHOD

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UDC 547.857.3'431.4:543.422

The reaction of bis(trimethylsilyl)hypoxanthine with methyl trichloromethyl ether has been investigated. 1-Methoxymethyl-, 7-methoxymethyl-, and 9-methoxymethylhypoxanthine, as well as 1,7-, 1,9-, and 3,7-bismethoxymethylhypoxanthine, have been isolated from the reaction mixture. The structures of the isomers have been established on the basis of an analysis of their UV, IR, ^{1}H NMR, ^{13}C NMR, and ^{15}N NMR spectra. The influence of the conditions under which the reaction is carried out on the yield of the alkylation products and the isomeric composition of the reaction mixture has been studied.

N-substituted derivatives of hypoxanthine are of interest both from a chemical and a biological point of view. It has been established that 9-(2-hydroxyalkyl)hypoxanthines, particularly erythro-9-(2-hydroxy-3-nonyl)hypoxanthine both in the individual state and in a complex with dimethylamino-2-propanol p-acetamidobenzoate, have antiviral, antileukotic, and immunomodulatory activity [2-4]. N-substituted hypoxanthines are also interesting objects for studying the mechanism of action of enzymes for nucleic acid metabolism and synthesis [5, 6].

In this context the development of effective methods for the synthesis of compounds of the class under consideration is a timely problem.

At the present time hypoxanthine derivatives are most often obtained from the corresponding derivatives of other 6-substituted purines, i.e., by the chemical or enzymatic deamination of N-substituted adenines [3, 7, 8] and by the alkaline or acid hydrolysis of 6-halo- [3, 9, 10] or 6-alkoxypurines [10]. These are usually complicated, multistep processes, which do not always make it possible to obtain the desired products with a sufficiently high yield.

The alkylation of hypoxanthine is seldom used for the synthesis of its derivatives. The methylation and benzylation of hypoxanthine by the corresponding alkyl halides produces a mixture of different mono- and bis-substituted derivatives, the ratio between the products being dependent on the structure of the alkylating agent, the pH of the reaction mixture, and the conditions under which the reaction is carried out (the solvent, temperature, etc.) [11-15]. The possibility of the migration of substituents during the alkylation of hypoxanthine has been demonstrated [16, 17].

The silyl alkylation method has not heretofore been used for the synthesis of nonglycoside derivatives of hypoxanthine; there are only data on the use of this method for obtaining inosine and some of its analogs [18-23].

When most investigators used this method [18-20, 23], the corresponding 9-substituted derivatives of hypoxanthine were isolated as the only product with a higher or lower yield; however, the formation of a mixture of 7- and 9-substituted products with predominance of the 7-isomer was noted in some cases [21, 22].

Our work was devoted to an investigation of the silyl method for the alkylation of hypoxanthine for the purpose of using it for the synthesis of N-alkoxyalkylhypoxanthines.

The alkylation of a silyl derivative of hypoxanthine by compounds such as alkyl, 2-haloethyl, and 2-acetoxyethyl halomethyl ether showed that a complex mixture of products forms

*For report 2, see [1].

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 518-524, April, 1986. Original article submitted July 3, 1985.

0009-3122/86/2204-0425$12.50

TABLE 1. UV and IR Spectra and Chromatographic Parameters of Hypoxanthine Derivatives III-VIII

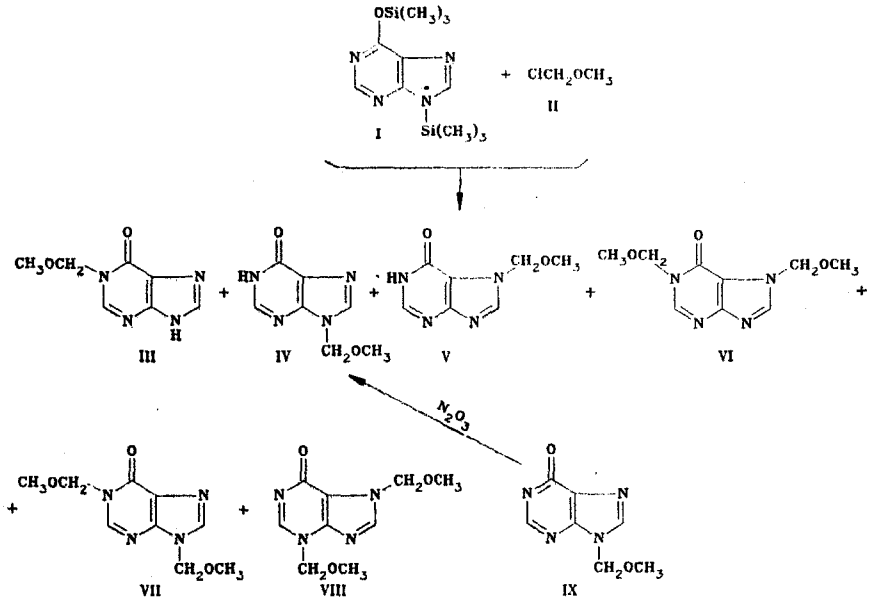
Compound	UV spectrum, λ_{max}, nm			IR spectrum, ν, cm^{-1} (in chloroform)			R_f	HPLC (relative retention volumes)
	pH 2	pH 7	pH 12	NH	C=O	C=O*		
III	250	251	262	3438	1708	1708	0,34	2,57
IV	250	250	255	3388	1690	1710	0,32	1,18
V	255	255	263	3390	1705	1680	0,31	1,00
VI	256	255	256	—	...	1700	0,62	1,65
VII	252	253	253	—	...	1700	0,71	2,00
VIII	263	266	266	—	...	1650	0,47	4,36

*In liquid petrolatum.

TABLE 2. Proton Chemical Shifts (ppm) in the PMR Spectra of Xanthine Derivatives III-VIII

Compound	8-H (S, 1H)	2-H (S, 1H)	NCH_2O (S, 2H)	CH, (S, 3H)	NH (S, 1H)
III	8,32	8,12	5,36	3,30	11,98
IV	8,25	8,10	5,50	3,28	12,46
V	8,42	8,02	5,66	3,27	12,45
VI	8,44	8,50	5,71, 5,41	3,30, 3,35	—
VII	8,31	8,50	5,54, 5,43	3,31, 3,35	—
VIII	8,43	8,50	5,71, 5,55	3,29, 3,34	—

during the reaction. Therefore, as a model reaction of the process under consideration we investigated the methoxymethylation of hypoxanthine by the silyl method.



The reaction of bis(trimethylsilyl)hypoxanthine (I) with methyl chloromethyl ether (II) gave a mixture of alkylation products. Their separation was carried out with the aid of fractional crystallization and preparative column chromatography on silica gel. In this manner we isolated 1- (III), 9- (IV), and 7-methoxymethylhypoxanthine (V), as well as 1,7- (VI), 1,9- (VII), and 3,7-bismethoxymethylhypoxanthine (VIII).

The determination of the individuality of the compounds obtained with the use of TLC is complicated by the similarity between the R_f values of the isomers in different solvent systems; therefore, HPLC served as the main method of determination (Table 1).

The establishment of the structure of compounds III-VIII, i.e., the determination of the position of the substituent in the purine ring, turned out to be a fairly complicated problem. A back synthesis by means of the deamination of 9-methoxymethyladenine (IX) gave compound IV and thereby proved that the structure corresponds to the 9-isomer. The structures of the remaining compounds synthesized were established on the basis of their UV, IR, and NMR spectra.

The UV spectra, which are usually used for the determination of the position of a substituent in a purine ring [24], was found to yield little information in this case due to the similar values of the absorption maxima of the isomeric N-substituted hypoxanthines; however, a comparison of the spectra of isomers III-VIII (Table 1) with the UV spectra of alkylhypoxanthines demonstrated that compound V has an absorption maximum at 255 nm, which is characteristic of the neutral molecules of 7-substituted hypoxanthines [24]. The UV spectrum of compound III corresponds more closely to the structure of 1-methylhypoxanthine than to 3-methylhypoxanthine [24], and the spectra of isomers VI, VII, and VIII correspond to the spectra of the 1,7-, 1.9, and 3,7-disubstituted hypoxanthines, respectively [12, 13, 24].

The vibrational frequency of the NH group of compound V in chloroform, i.e., 3390 cm^{-1} (Table 1), corresponds exactly to ν_{NH} in 7-methylhypoxanthine [25], and the frequencies of the ν_{NH} (3438 cm^{-1}) and $\nu_{C=O}$ (1708 cm^{-1}) vibrations of isomer III are evidence in support of the structure of 1-methoxymethylhypoxanthine for this compound.

The structures of the alkylation products of hypoxanthine were unequivocally established with the aid of ^1H, ^{13}C, and ^{15}N NMR, as well as the ^{13}C spectra without decoupling from the protons and ^{13}C spectra with selective suppression of individual ^1H signals (Tables 2-4). As is seen from the data in Table 2, the ^1H chemical shifts provide little information to prove the structures of the isomers. In the case of 1,7- and 3,7-disubstituted products VI and VIII, an unequivocal assignment is totally impossible.

The ^{13}C NMR spectra proved to be far more informative. The presence of characteristic values of the long-range $^{13}C-^1H$ spin–spin interaction in the hypoxanthine ring (Table 3) makes it possible to unequivocally assign all the ^{13}C signals. The site of substitution is also proved by utilizing the long-range spin–spin coupling with the protons of the NCH_2 group, as was described in [26]. A difference in the spectral behavior of bis-substituted products VI and VIII, whose ^1H NMR spectra were identical, was thus detected.

The ^{15}N NMR spectra could also be obtained for some of the compounds (IV-VII), and the ^{15}N chemical shifts for all four nitrogen atoms of the purine ring could then be established (Table 4). The changes in the ^{15}N chemical shifts of hypoxanthine under the influence of the substituents are similar to those found in methylated purines [27].

We next investigated the influence of the conditions for carrying out the methoxymethylation of hypoxanthine on the regioselectivity and yield of the alkylation products, the isomeric composition of the mixtures obtained being determined by HPLC with the use of the previously isolated compounds III-VIII as markers.

When compounds I and II were reacted in dichloroethane at room temperature, it was found that the alkylation yield reaches 30%, of which ~75% is made up of 1-substituted isomer III, and ~25% is made up of 9-substituted isomer IV. Traces of compounds V, VI, and VII (1-3%) were also discovered among the alkylation products.

When the alkylation of I was carried out in the absence of a solvent at an elevated temperature (at the fusion point), the extent of conversion of I amounted to 60%; however, the isomeric composition of the reaction mixture changed significantly, i.e., the percentage of disubstituted isomers VI and VII increased sharply (to 50% of the total yield of the alkylation products). The second half of the products was made up of 7- and 9-isomers V and IV in a 1.5:1 ratio. Compound III was present only in trace amounts ($\leq$2%).

A mixture of IV and V was obtained as the main alkylation product both when the reaction was carried out in the presence of an equimolar quantity of triethylamine (IV:V = 1:5.5; the yield was 10%) and when tin(IV) chloride in an amount equal to 1.5 eq was employed as a catalyst (IV:V = 1:1.5). In the latter case, the yield of the alkylation reaction was high (60%); however, the reaction mixture also contained VI and VII and an admixture of isomer III.

Since there are data [28] indicating that an excess of the silylating agent and the secondary silylation products influence the course of a glycosylation process, the reaction of compounds I and II was also carried out without distilling off the excess of hexamethyldisilazine, which was employed as the silylation agent. The yield of the alkylation products did

TABLE 3. ^{13}C NMR Spectra of Compounds III-VIII

Compound	Chemical shifts, δ, ppm						
	CH_2	CH	$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(8)}$
III	75,84	56,24	147,64	152,99	118,12	154,81	141,11
IV	73,85	56,32	146,13	148,66	124,07	156,72	140,73
V	76,27	55,65	144,78	157,34	114,81	154,09	144,47
VI	76,47 ($N_{(7)}$), 75,76 ($N_{(1)}$)	55,76 ($N_{(7)}$), 56,28 ($N_{(1)}$)	147,99	156,94	114,13	153,60	145,42
VII	73,85 ($N_{(9)}$), 76,03 ($N_{(1)}$)	56,37, 56,37	149,01	148,00	123,33	156,11	141,34
VIII	75,93 ($N_{(7)}$), 78,28 ($N_{(3)}$)	56,54 ($N_{(7)}$), 55,89 ($N_{(3)}$)	148,64	144,65	113,62	161,92	143,22

Compound	$^{13}C-^{1}H$ spin–spin coupling constant, J, Hz							
	$C_{(2)}-H_{(2)}$	$C_{(8)}-H_{(8)}$	$C_{(4)}-H_{(2)}$	$C_{(6)}-H_{(2)}$	$C_{(5)}-H_{(8)}$	$C_{(4)}-H_{(8)}$	$C_{(6)}-H_{(8)}$	$C_{(x)}-CH_2$
III*	207,4	210,7	...	5	...	...	...	5,1 $C_{(2)}$, 2,8 $C_{(6)}$
IV	203,5	211,4	14,2	7,1	11,1	4,9	0,9	4,2 $C_{(8)}$, 3,3 $C_{(4)}$
V	205,7	211,8	13,3	7,2	4,1	13,3	0,8	4,6 $C_{(8)}$, 1,5 $C_{(5)}$
VI	208,3	212,4	14,0	6,2	3,9	12,9	1,1	5,0 $C_{(2)}$, 3,2 $C_{(6)}$, 4,6 $C_{(8)}$, 3,3 $C_{(5)}$
VII	208,6	214,4	8,3	6,0	11,2	4,6	0,9	2,9 $C_{(4)}$, 4,2 $C_{(8)}$, 3,2 $C_{(6)}$, 5,3 $C_{(2)}$
VIII	206,5	214,2	7,8	12,2	4,4	13,2	0,6	3,0 $C_{(5)}$, 4,6 $C_{(8)}$, 5,1 $C_{(2)}$, 3,6 $C_{(4)}$

*The signals from the $C_{(4)}$ and $C_{(5)}$ carbons are strongly broadened, and the constants of the spin–spin interactions involving them could not be determined.

TABLE 4. Chemical Shifts of Nitrogen Atoms (ppm) in the ^{15}N NMR Spectra of Compounds IV-VII

Compound	$N_{(1)}$	$N_{(3)}$	$N_{(7)}$	$N_{(9)}$
Inosine*	−206,9	−167,4	−132,9	−206,9
IV	−206,5	−166,7	−131,7	−206,5
V	−208,6	−147,2	−212,0	−129,2
VI	−197,5	−145,4	−211,0	−129,0
VII	−195,1	−175,2	−130,7	−208,1

*According to data in [29].

not decrease in this case (45-50%), and a mixture of the 7- and 9-isomers (V:IV = 1.5:1) was also isolated as the main product of the reaction; however, disubstituted products VI and VII and isomer VIII, which made up 5-10% of the total quantity of the alkylation products, were obtained along with them.

Isomers VI and VIII were found to be unstable compounds when they were isolated in their pure forms. Under the conditions for obtaining the ^{13}C and ^{15}N spectra (broad-band suppression of the interaction with the protons, a temperature of the samples equal to 40°C, and dimethyl sulfoxide as the solvent) 1,7-disubstituted hypoxanthine VI was converted into an equilibrium mixture of 1,7- and 1,9-isomers VI and VII, as follows from the data from the ^{13}C NMR spectra. Since an equilibrium mixture of VI and VII was also obtained in the case of samples containing $\geq$70% 1,9-bis-substituted product VII and $\leq$30% 1,7-disubstituted product VI, it may be postulated that migration of the substituent between positions 7 and 9 of the purine ring occurs in a dimethyl sulfoxide solution.

3,7-Bisubstituted hypoxanthine VIII was also converted into a mixture of 1,7 and 1.9 isomers VI and VII under similar conditions; therefore, the kinetically more advantageous substitution in position 3 turns out to be thermodynamically unadvantageous, and migration of the substituent to position 1 of the purine ring occurs.

The investigation which we carried out showed that the methoxymethylation of hypoxanthine by the silyl method can be used when appropriate conditions for carrying out the reaction are selected for the preparative synthesis of 1-, 7-, and 9-methoxymethylhypoxanthine, as well as 1,7- and 1,9-bismethoxymethylhypoxanthine.

The 7- and 9-monosubstituted reaction products and the disubstituted reaction products were also isolated by us in the case of the alkylation of compound I by other α-halo ethers (by alkyl chloromethyl ethers and by 2-acetoxy- and 2-chloroethyl chloromethyl ether). More detailed investigations of the influence of the alkylating agent on the regiospecificity and the yield of the alkylation of hypoxanthine by the silyl method are being continued.

EXPERIMENTAL

The UV spectra were recorded on a Unicam-SP 1800 spectrophotometer, and the IR spectra were recorded on a UR-20 instrument. The ^1H NMR spectra were obtained on a Bruker WH-90/DS spectrometer (90 MHz) in DMSO-D_6 with TMS as an internal reference, the accuracy of the measurements of the chemical shifts being ±0.01 ppm. The ^{13}C and ^{15}N spectra were recorded on a Bruker WM-360 spectrometer at 90.5 and 36.5 MHz, respectively. The chemical shifts in the ^{13}C NMR spectra were measured relative to the signal of the solvent DMSO-D_6 and were recalculated with respect to tetramethylsilane (δ = 39.6 ppm). The ^{15}N chemical shifts were measured relative to the external reference nitromethane. The accuracy of the measurement of the ^{13}C chemical shifts was ±0.03 ppm, and that for the ^{15}N chemical shifts was ±0.1 ppm. The accuracy of the measurement of the $^{13}C-^1H$ spin–spin coupling constants was ±0.1 Hz. The purity of the compounds obtained was monitored by TLD on Silufol UV-254 plates in a 10:1 chloroform–methanol solvent system. Silica Gel L 40/100 (from Czechoslovakia) was used for the preparative column chromatography. The separation of the isomers by HPLC was carried out on a Du Pont model 850 liquid chromatograph in a column measuring 4.6 × 130 mm filled with the sorbent Silasorb C 18 4C (Czechoslovakia) with a particle diameter equal to 5 μ. A mixture of acetonitrile, acetic acid, and a 0.02 M solution of sodium dodecylsulfonate in a 15:2.5:82.5 ratio served as the mobile phase, and the time for an analysis was 5 min.

1-Methoxymethylhypoxanthine (III). A mixture of 5.0 g (37 mmoles) of hypoxanthine and 30 ml of hexamethyldisilazane is boiled until the hypoxanthine dissolves completely. The excess hexamethyldisilazane is distilled off in a vacuum, product I obtained is dissolved in 30 ml of dichloroethane, and 2.98 g (37 mmoles) of II are added. The solution is stirred at room temperature for 5 days, cooled to 0°C, and given an addition of 40 ml of ethanol. The mixture is stirred at room temperature for 1 h and evaporated in a vacuum. The residue is extracted by 180 ml of a boiling 10:2 chloroform–ethanol mixture. The extract is evaporated, and the residue is dissolved in chloroform (30 ml) with heating. The insoluble precipitate, which consists mainly of product III, is filtered and recrystallized from ethanol. An additional quantity of III is isolated from the chloroform solution with the aid of column chromatography on silica gel. Product III is eluted by a 2:1 chloroform–methanol mixture after the separation of the fractions containing isomer IV.

The total yield of compound III was 1.49 g (22.5%), mp 205.5-206.5°C. Found: C 46.7; H 4.6; N 30.9%. Calculated for $C_7H_8N_4O_2$: C 46.7; H 4.5; N 31.1%.

9-Methoxymethylhypoxanthine (IV) and 7-Methoxymethylhypoxanthine (V). A. A 4.0-g portion (29 mmoles) of hypoxanthine with 25 ml of hexamethyldisilazane is boiled until the hypoxanthine completely dissolves. The solution is given an addition of 20 ml of dichloroethane and 2.34 g (29 mmoles) of II and storred at room temperature for 4 days. After cooling to ~0°C, the reaction mixture is given an addition of 30 ml of ethanol, stirred for 1 h at room temperature, and evaporated in a vacuum. The residue is extracted by 120 ml of a boiling 10:2 chloroform–methanol mixture, the extract is evaporated in a vacuum, and the residue is dissolved in chloroform (30 ml) with heating. The insoluble precipitate, which consists mainly of product V, is filtered out and recrystallized from ethanol. An additional quantity of V, as well as compound IV, are isolated from a chloroform solution by column chromatography on silica gel. After the removal of disubstituted isomers VI-VIII by chloroform, IV and V are eluted by a 20:1 chloroform–methanol mixture. This gives 1.15 g (22%) of V (mp 215-217°C. Found: C 46.4; H 4.7; N 31.0%. Calculated for $C_7H_8N_4O_2$: C 46.7; H 4.5; N 31.1%) and 0.80 g (15.3%) of IV (T_m 205.5-207°C. Found: C 46.9; H 4.7; N 31.2%. Calculated for $C_7H_8N_4O_2$: C 46.7; H 4.5; N 31.1%).

B. Silyl derivative I, which is obtained from 1.0 g (7.3 mmoles) of hypoxanthine, as described in the synthesis of III, is dissolved in 50 ml of dichloroethane and given an addi-

tion of 0.59 g (7.3 mmoles) of II and a solution of 1.3 ml (11 mmoles) of tin(IV) chloride in 10 ml of dichloroethane. The solution is stirred at room temperature for 24 h. Then it is cooled to ~0°C, given an addition of a mixture consisting of 25 ml of ethanol and 5 ml of triethylamine, stirred at room temperature for 1 h, and evaporated in a vacuum. The residue is extracted by 55 ml of a boiling 10:1 chloroform–methanol mixture. The extract is concentrated to a minimal volume and introduced into a column with silica gel. After the removal of disubstituted isomers VI and VII by chloroform, compounds IV and V are eluted by a 20:1 chloroform–methanol mixture. This gives 0.41 g (31%) of V and 0.25 g (19%) of IV.

1,7-Bismethoxymethylhypoxanthine (VI). Silyl derivative I, which is obtained from 5.0 g (37 mmoles) of hypoxanthine as described in the synthesis of III, is given an addition of 2.98 g (37 mmoles) of II. The reaction mixture is held at 110-120°C for 45 min and then cooled to ~0°C and given an addition of 40 ml of ethanol. The mixture is stirred at room temperature for 1 h and evaporated in a vacuum. The residue is extracted by chloroform (100 ml), and the extract is concentrated to a minimal volume and introduced into a column with silica gel. Product VI is eluted by chloroform after the separation of the fractions containing mainly up to 70%) product VII. Recrystallization from ethanol gives 1.16 g (14%) of isomer VI, mp 104°C. Found: C 48.1; H 5.4; N 25.3%. Calculated for $C_9H_{12}N_4O_3$: C 48.2; H 5.4; N 25.0%.

3,7-Bismethoxymethylhypoxanthine (VIII) is obtained with a 5-8% yield by separating the chloroform extract obtained as described in the synthesis of compounds IV and V (method A) in a column with silica gel. Isomer VIII is eluted by chloroform after the separation of the fractions containing products VI and VII. Mp 110-111°C. Found: C 48.5; H 5.5; N 24.9%. Calculated for $C_9H_{12}N_4O_3$: C 48.2; H 5.4; N 25.0%.

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ALKYLIMINOMALONIC ACID AND 2-ALKYLOXAZIRIDINE-3,3-DICARBOXYLIC ACID ESTERS*

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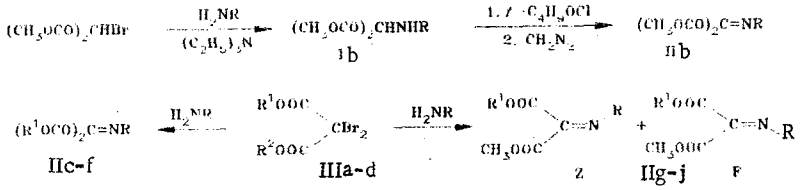
UDC 547.717.04:541.632:543.422

2-Alkyloxaziridine-3,3-dicarboxylic acid esters have been obtained by oxidizing alkylaminomalonic acid esters by monoperphthalic acid. The activation parameters for the inversion of the nitrogen atom have been obtained for a number of alkyliminomalonic acid and 2-alkyloxaziridine-3,3-dicarboxylic acid ester.

The introduction of geminal esteric groups in the α position to a configurationally stable nitrogen atom made it possible to develop a general method for the separation of 1-alkoxyaziridine-2,2- [2]-, 1-alkyldiaziridine-3,3- [3], and 2-alkoxyisoxazolidine-3,3-dicarboxylic acid esters [4], which contain only a nitrogen chiral center, into antipodes. It would be of interest to extend this method to other nitrogen-containing heterocycles, particularly to oxaziridines, whose chiral derivatives were previously obtained only by asymmetric reactions involving the oxidation of imines [5]. However, oxaziridines with electron-acceptor functional groups on the C atom were not known until very recently. The report of the syntheses of 2-phenyl-3,3-dibenzoyloxaziridine by the photoisomerization of N-phenyl-α,α-dibenzoylnitrone and the oxidation of the anil of diphenyl triketone in [6] proved to be erroneous [7]. We developed methods for the synthesis of alkyliminoamlonates and the first oxaziridines with functional groups on the C atom.†

Alkyliminomalonates IIa-j were obtained on the basis of mono- and dibromomalonates according to the schemes



I, II a R=CH_3, b R=C_2H_5; II c, d, g, i R=i-C_3H_7, d, f, h, j R=t-C_4H_9; c, d R^1=CH_3, e, f, g, h R^1=C_2H_5, i, j R^1=i-C_3H_7; III a, c, d R^1=CH_3, b R^1=C_2H_6; a R^2=CH_3, b, c R^2=C_2H_5; d R^2=i-C_3H_7

Imines IIa and b cannot be obtained by reacting n-alkylamines with dibromomalonic ester, since exhaustive amidation is observed in this case [8]. It must be noted that imines IIa and b, unlike the remaining imines, are unstable and polymerize completely during storage over the course of 1 month.

When imines IIa-j are oxidized by monoperphthalic acid, they form the corresponding oxaziridines IVa-j with good yields:

*Report 46 from a series entitled Asymmetric Nonbridging Nitrogen. For report 45 see [1].
†For the preliminary report see [8].

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0009-3122/86/2204-0431$12.50