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On the Reactions of Oxazolium Salts with Dialkyl Acylphosphonates.[1] A Novel Synthesis of 1,4-Oxazin-3-one and Azetidin-2-one Derivatives

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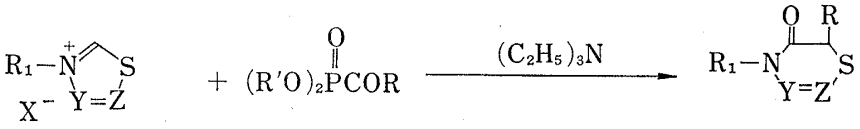
Reaction of Oxazolium salts (IX) with dialkyl acylphosphonates (IV) in the presence of triethylamine afforded 1,4-oxazin-3-one (XII) and/or azetidin-2-one derivatives (XIII). In the reaction of IXa—b with IVa, stable reaction intermediates (Xa—b) were isolated. Some of the products were confirmed to be identical with authentic samples synthesized by an independent pathway. The mechanism of this novel reaction involving ring expansion and ring contraction, substituent effects on the reactivity, and stereochemistry of XIII are discussed.

We have previously reported that thiazolium (I), 1,3,4-thiadiazolium (II), and 1,2,4-thiadiazolium salts (III) react with dialkyl acylphosphonates (IV) to give the ring-expanded products, 1,4-thiazine (V),[3] 1,3,4-thiadiazine (VI),[4] and 1,2,4-thiadiazine derivatives (VII),[5] respectively.



IV

I : Y=C−R₂, Z=C−R₃
II : Y=N, Z=C−R₃
III : Y=C−R₂, Z=N

V : Y=C−R₂, Z=C−R₃
VI : Y=N, Z=C−R₃
VII : Y=C−R₂, Z=N

R =alkyl, aralkyl, and aryl
R₁=alkyl and aralkyl
R₂=alkyl or aryl
R₃=alkyl or aryl

Chart 1

In order to extend the scope of the reaction, application was directed toward some oxazolium salts, and the present paper is concerned with these results.

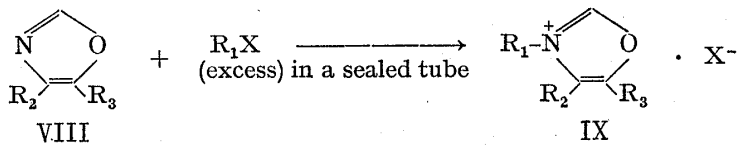
Since Haake, *et al.*[6] had shown that the base-catalyzed deprotonation of the C_2–H of 3,4-dimethyloxazolium iodide proceeds 100 times faster than that of 3,4-dimethylthiazolium iodide in acetate buffers at 33.5°, it seemed reasonable to expect that oxazolium salts might serve also as very reactive materials toward dialkyl acylphosphonates.

1) This paper constitutes Part LXXXV of a series on Studies on Pyrimidine Derivatives and Related Compounds. Part LXXXIV. A. Takamizawa, S. Matsumoto, and I. Makino, *Chem. Pharm. Bull.* (Tokyo), **22**, 311 (1974).
2) Location: *Fukushima-ku, Osaka, 553, Japan.*
3) A. Takamizawa, Y. Hamashima, and H. Sato, *J. Org. Chem.*, **33**, 4038 (1968); A. Takamizawa, H. Sato, and Y. Sato, *Chem. Pharm. Bull.* (Tokyo), **20**, 892 (1972).
4) A. Takamizawa, H. Sato, *Chem. Pharm. Bull.* (Tokyo), **18**, 1201 (1970).
5) A. Takamizawa and H. Harada, *Chem. Pharm. Bull.* (Tokyo), **18**, 1402 (1970).
6) P. Haake, L.P. Bausher, and W.B. Miller, *J. Amer. Chem. Soc.*, **91**, 1113 (1969).

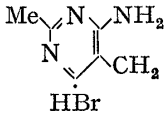
Preparation of Oxazolium Salts

Various oxazoles (VIII) were prepared according to the literature, and by quarternization with the appropriate alkyl halides the corresponding oxazolium salts (IX) were obtained (Table I).

Table I. Preparation of Oxazolium Salts

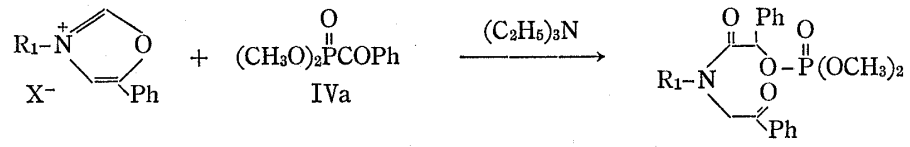


VIII IX

React. No.	Literature of VIII	React. temp. (°C)	React. time. (hr)	Note	Products: Compd. No.	R_1	R_2	R_3	X	mp (°C)	Yield (%)
1	*a*)	110	100	atmosp. pressure	IXa	$PhCH_2$	H	Ph	Cl	192—194 (d.)	79
2	*a*)	95—100	24		IXb	Me	H	Ph	I	180—182 (d.)	71
3	*b*)	105	18.5		IXc	Me	Me	Ph	I	185—186	77
4	*c*)	100	26.5		IXd	Me	Ph	Ph	I	187—188	83
5	*b*)	105—107	19		IXe	Me	Ph	Me	I	138—140	81
6	*c*)	65	31.5	atmosp. pressure, in DMF	IXf		Et	Et	Br	240—242 (d.)	57

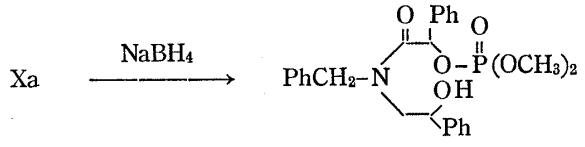
literature of VIII *a*) C. Tanaka, *Yakugaku Zasshi*, **85**, 186 (1965). *b*) H. Bredereck and R. Gompper, *Chem. Ber.*, **87**, 700 (1954). *c*) H. Bredereck and R. Gompper, *Chem. Ber.*, **87**, 726 (1954).

Reactions of 3-Benzyl(or Methyl)-5-phenyloxazolium Salts (IXa or IXb) with Dimethyl Benzoylphosphonate (IVa)



IXa: R_1=$PhCH_2$, X=Cl
IXb: R_1=CH_3, X=I

Xa: R_1=$PhCH_2$
Xb: R_1=CH_3



XIa: mp 148—150°
XIb: mp 125—128°

Ph=phenyl

Chart 2

3-Benzyl-5-phenyloxazolium chloride (IXa) reacted with dimethyl benzoylphosphonate (IVa) inN,N-dimethylformamide (DMF) in the presence of triethylamine (Et_3N) at −50——60° to give a colorless crystalline product (Xa) of mp 135—140° in 74% yield. The elementary analysis of Xa was in agreement with the composition $C_{25}H_{26}O_6NP$, and its mass spectrum exhibited a molecular ion peak at *m/e* 467, suggesting that Xa is a 1:1 adduct (free base) of IXa and IVa. The infrared (IR) spectrum (nujol) of Xa showed two C=O bands at 1700 and 1676, a P=O band at 1270, and P–O–C bands at 1043 and 1014 cm^{-1}, but no hydroxyl

absorption band was observed; its ultraviolet (UV) spectrum in ethanol showed an absorption maximum at 244.5 mμ (log ε 4.17). The nuclear magnetic resonance (NMR) spectrum taken at room temperature in d_6-DMSO (Fig. 1-A) showed signals for two methoxyl protons (τ 6.46, d, J_{PH}=11.0 Hz; τ 6.36, d, J_{PH}=11.0 Hz), three phenyl protons (τ 2.8—2.0, multiplet), benzylic protons at τ 5.46, 5.07 as an AB-quartet (J=17.8 Hz), and methylene protons at τ 5.46 as a broad singlet in addition to a characteristic 1H at τ 3.92 and 3.82 as two doublets (J=7.8 Hz) due to hydrogen-phosphorus coupling, respectively. Temperature dependence of the spectrum was observed at 90°, at which temperature each signal pattern had sharpened and simplified (Fig. 1-B), and at 120°, where the two doublet signals at τ 3.92 and 3.82 collapsed to one doublet signal at τ 3.92 (Fig. 1-C), though hardly any difference in the coupling constant of this 1H-signal was discernible at any temperature. These results suggest the structure O-[1-phenyl-2-oxo-2-(N-phenacyl-N-benzylamino)ethyl]-O,O-dimethylphosphate for product Xa, and on the basis of the intensities of the above two doublet signals, the broadening of each signal in the spectrum taken at room temperature (Fig. 1-A), and the temperature dependence of the spectrum (Fig. 1-B and C), it is probably a mixture of isomers in a ratio of about 1:2 resulting from rotational inhibition around the C–N bond of the N–C=O group.[7]

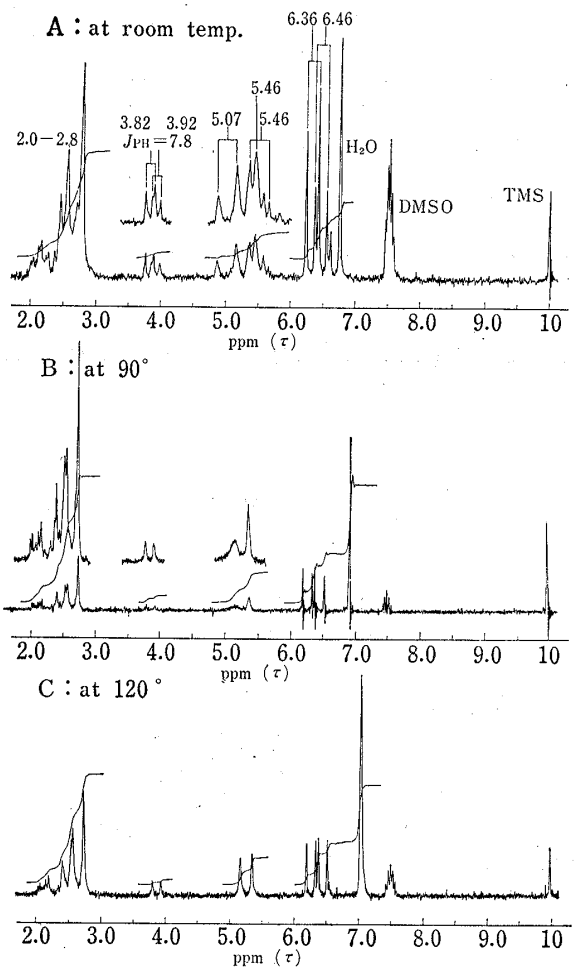


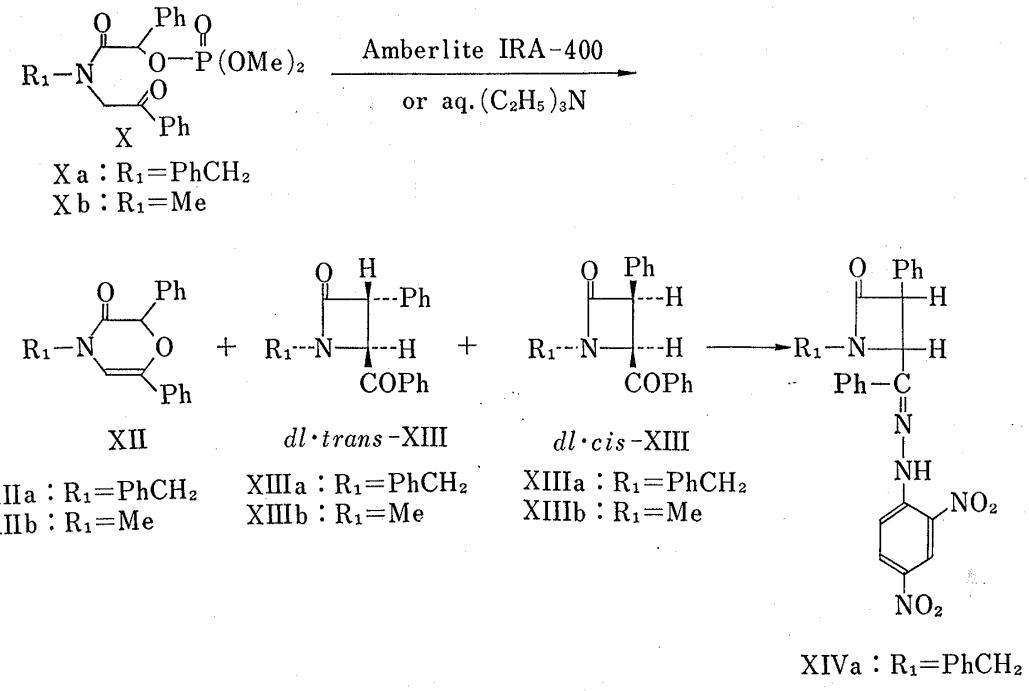
Fig. 1. NMR Spectra of Xa in d_6-DMSO at Different Temperatures

The reaction of 3-methyl-5-phenyloxazolium iodide (IXb) with IVa similarly gave a 1:1 adduct (Xb) as an oil in 31.2% yield.

$NaBH_4$ reduction of Xa in MeOH gave compound XIa, mp 148—150°, and compound XIb, mp 125—128°, in 52.2% and 27.6% yield, respectively. These compounds have the same constitution, $C_{25}H_{28}O_6NP$. In their UV spectra, the absorption maximum at 244.5 mμ seen for Xa was absent. The IR spectra of both compounds (in CCl_4, 4×10^{-4} mole/liter) showed bands for N–C=O, P=O, and P–O–C bonds, but the ketonic C=O band seen at 1700 cm^{-1} for Xa was not observed. Absorption bands due to a secondary hydroxyl group, however, were newly observed at 3389 cm^{-1} for XIa and at 3431 and 3353 cm^{-1} for XIb. These results, together with the ratio in the formation of products suggest that XIa and XIb are isomers of O-[1-phenyl-2-oxo-2-{N-(2-hydroxy)phenethyl-N-benzylamino}ethyl]-O,O-dimethylphosphate due to rotational inhibition around the C–N bond of the N–C=O group.[7]

When Xa was treated with a strongly basic ion exchange resin, Amberlite IRA-400, in methanol at room temperatures, three compounds containing no phosphorus atom, XIIa, mp 106—109°, *dl*·*trans*-XIIIa, mp 111—113°, and *dl*·*cis*-XIIIa, mp 186—188°, were produced in 34.6, 14.0 and 5.2% yield, respectively. Compound XIIa was readily assigned as 2,6-diphenyl-4-benzyl-2,3-dihydro-4H-1,4-oxazin-3-one, a compound whose

7) L.A. Laplanche and M.T. Rogers, *J. Am. Chem. Soc.*, **86**, 337 (1964); *idem*, *ibid.*, **85**, 3728 (1963).



Ph=phenyl Chart 3

formation was expected from the reaction behavior of other azolium salts reported previously,[3-5] on the basis of the following data. Elemental analysis of XIIa gave the formula as $C_{23}H_{19}O_2N$. Its UV spectrum showed a strong absorption maximum at 310 mμ (log ε 4.13) in ethanol, and its IR spectrum exhibited a strong carbonyl band at 1681 cm^{-1} (N–C=O) in chloroform. The NMR spectrum showed signals at τ 5.14 (s, 2H, NCH_2), 4.25 (s, 1H, C_2–H), and 3.87 (s, 1H, C_3–H) in addition to aromatic proton signals (15H) in the usual place.

The constitutions of the compounds *trans*-XIIIa and *cis*-XIIIa are same as that of XIIa, but their UV spectral patterns [λ_{max}^{EtOH} mμ (log ε): *trans*-XIIIa, 250 (4.13); *cis*-XIIIa, 251.5 (4.07)] differ from that of XIIa suggesting a fundamental difference in the skeleton. The IR spectra ($CHCl_3$) showed two carbonyl bands at 1758 and 1692 cm^{-1} for *trans*-XIIIa, and at 1756 and 1692 cm^{-1} for *cis*-XIIIa. For both *trans*- and *cis*-XIIIa, therefore, a strained ring structure, *i.e.*, a β-lactam ring formed by cyclization of the methylene carbon adjacent to the benzoyl group in Xa, was suggested on the basis of the higher wavenumber value observed in either case. On addition of 2,4-dinitrophenylhydrazine to an acidic ethanolic solution of *cis*-XIIIa, the corresponding hydrazone XIVa, mp 199—200°, was obtained showing that *cis*-XIIIa has a benzoyl group out of the ring. Based on these and the following NMR spectral data it was concluded that *trans*- and *cis*-XIIIa are configurational isomers of 1-benzyl-3-phenyl-4-benzoylazetidin-2-one arising from the substituent groups on the β-lactam ring.

The configurations of these compounds were elucidated on the basis of NMR spectral data (Fig. 2). It is already known in the NMR spectra of 1,3,4-trisubstituted azetidin-2-ones that the magnitude of the vicinal coupling constant between *cis* C_3–H and C_4–H (4.9—5.9 Hz) is greater than that between *trans* protons (2.2—2.8 Hz), that an N-substituent (H, CH_3 or $C_6H_5CH_2$) lying on the opposite side of the β-lactam ring to the C_4-substituent long-range couples with C_3–H through a transoid pathway, and that the benzylic protons in N-benzyl compounds show marked magnetic non-equivalence.[8] Now in our XIIIa compounds the coupling constant between C_3–H and C_4–H was greater in the *cis*-compound (J=6.0 Hz) than in the

8) K.D. Barrow and T.M. Spotswood, *Tetrahedron Lett.*, **1965**, 3325; H.B. Kagan, J.-J. Basselier, and J.-J. Luche, *ibid.*, **1964**, 941.

trans-compound (J=2.6 Hz); stereospecific cross-ring coupling (J=0.8 Hz) between the higher field benzylic proton and C_3–H was observed with *trans*- but not with *cis*-XIIIa; and the *trans*-compound exhibited diamagnetic shielding by the C_3 and C_4 substituents of the respective neighbouring C_4 and C_3 protons, that is, the chemical shifts for the C_3 and C_4 protons were at higher fields in the *trans*- than in the *cis*-compound. From these facts we could completely determine the configurations of the substituents on the β-lactam ring, as shown in Chart 3.

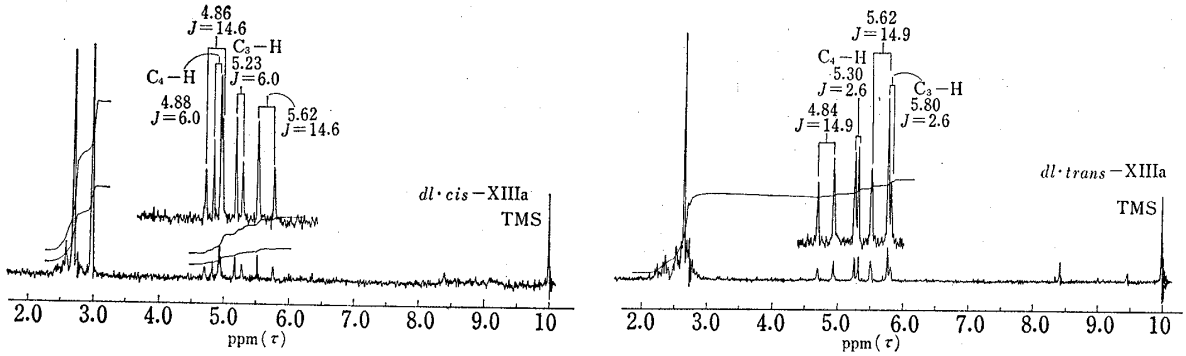


Fig. 2. NMR Spectra of *dl*·*trans*-XIIIa and *dl*·*cis*-XIIIa in $CDCl_3$

Cannon, *et al.*[9] obtained 1,4-oxazin-3-one XVI by treating amide XV with Amberlite IRA-400. On the other hand, Chatterjee, *et al.*[10] reported the formation of azetidin-2-one XVIII from amide XVII by treating with alcoholic potassium hydroxide. We have tried the former reaction with amides XIX. For example, on treatment of amide XIXa, prepared by the reaction of monophenacylbenzylamine hydrochloride with α-chlorophenylacetyl chloride in the presence of sodium acetate, with the above basic ion exchange resin, the three compounds XIIa, *trans*-XIIIa, and *cis*-XIIIa were simultaneously obtained in yields corresponding to those from Xa. This gave chemical evidence for the structures of XIIa, *trans*-XIIIa, and *cis*-XIIIa, while in addition providing useful information on the mechanism of formation of these compounds from X.

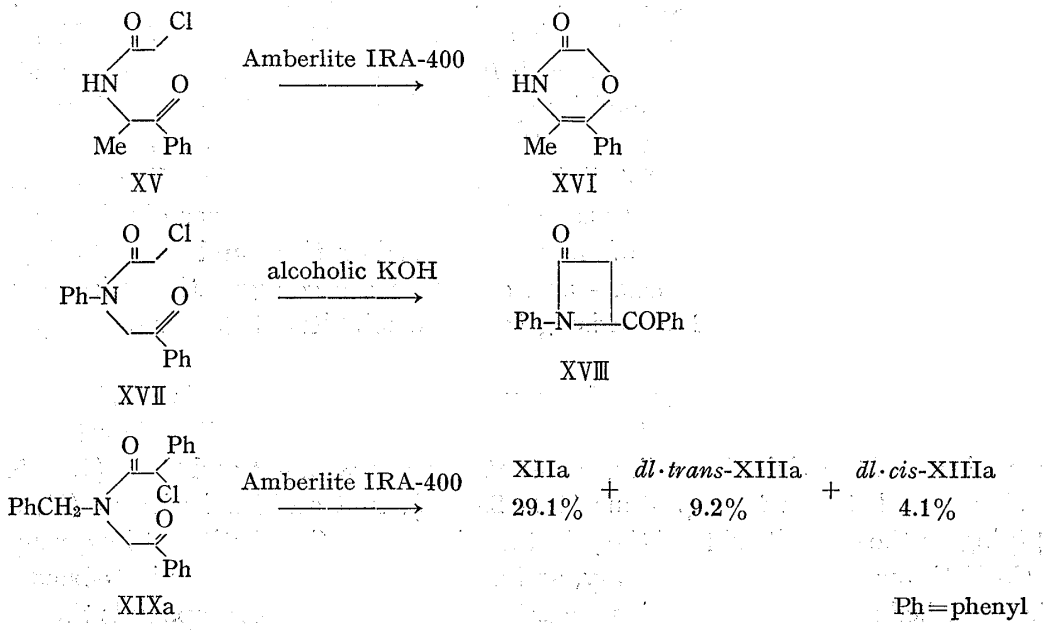


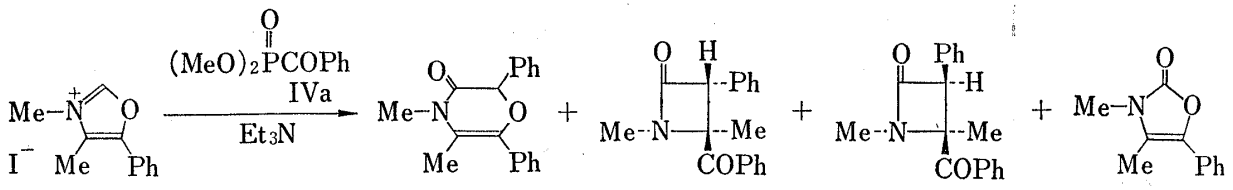
Chart 4

9) W.F. Cannon, Evanston, III, and G.I. Poos, U.S. Patent, 3308121 (1967).
10) B.G. Chatterjee, V.V. Rao, S.K. Roy, and H.P.S. Chawla, *Tetrahedron*, 23, 493 (1967).

Similarly, when Xb was treated with Amberlite IRA-400, the corresponding products XIIb, *dl*·*trans*-XIIIb and *dl*·*cis*-XIIIb were obtained (see Experimental section and Chart 3).

Reaction of 3,4-Dimethyl-5-phenyloxazolium Iodide (IXc) with Dimethyl Benzoylphosphonate (IVa)

TABLE II. Reaction of 3,4-Dimethyl-5-phenyloxazolium Iodide (IXc) with IVa



IXc XIIc *dl* · *trans*[a]-XIIIc *dl* · *cis*[a]-XIIIc XXc

	XIIc	*dl trans*-XIIIc	*dl cis*-XIIIc	XXc
mp (°C)	146—150	129—131	161—163	120—123
λ_{max}^{EtOH} mμ (log ε)	300 (3.96)	247.5 (4.09)	249.5 (4.04)	278 (4.26)
$\nu_{C=O}^{CHCl_3}$ cm^{-1}	1675	1754, 1686	1756, 1685	1750
NMR ($CDCl_3$)	C_3–H, τ 4.46 (s)	C_4–Me, τ 8.57 (s)	C_4–Me, τ 8.12 (s)	N-Me, τ 6.78 (s)
	C_5–Me, τ 7.94 (s)	J_{N-Me,C_3-H} 0.8 Hz	J_{N-Me,C_3-H} OHz	C_4–Me, τ 7.73 (s)
Yield[b] (%)	0.5	6.2	5.6	0.3

a) configuration with respect to N–Me and C_3–H
b) yields after preparative thin-layer chromatography on Al_2O_3(ether) and $Al_2O_3(CHCl_3)$

This novel reaction was tried with oxazolium salt IXc having an electron-releasing methyl group at the C_4-position, one of the reactive centers in the reaction with IXa—b. The reaction was carried out under the same conditions as described above using IVa. The reaction mixture gave 1,4-oxazin-2-one XIIc, azetidin-2-one XIIIc (*dl*·*trans* and *dl*·*cis*), and oxazol-2-one XXc as a by-product on concentration followed by treatment with Amberlite IRA-400, without isolation of the intermediate corresponding to Xa—b. The product distribution in this reaction (see Table II), in which contrary to our expectations the predominating product was XIIIc (*trans* and *cis*), suggested that a C_4-substituent affects the reactivity sterically rather than electronically, a point which will be further dealt with later. The structures of these products were confirmed by their analytical and spectral data, which are shown in the Experimental section and in Table II, and the stereochemistry of *trans*-XIIIc and *cis*-XIIIc were substantiated on the basis of NMR observation of the existence of long-range coupling between N–CH_3 and C_3–H and of the magnetic anisotropy effect of the C_3–C_6H_5 group on C_4–CH_3 protons (see Table II).

Reactions of 3-Methyl-4,5-diphenyloxazolium Iodide (IXd) with Dialkyl Acylphosphonates (IVb and IVa′)

When 3-methyl-4,5-diphenyloxazolium iodide (IXd) was allowed to react with dimethyl acetylphosphonate (IVb), a 1,4-oxazin-3-one XIId as a major product, accompanied by an azetidin-2-one *dl*·*cis*-XIIId as a minor product was obtained. However, when IXd was treated with diethyl benzoylphosphonate IVa′, no formation of a 1,4-oxazin-2-one derivative corresponding to XIId was observed. Consequently, these results shown the marked effect of the acyl substituent of phosphonates IV on the reaction direction of IXd. Further comment on this aspect will be made later. The structures of unknown products were confirmed by identification with authentic samples synthesized by independent cyclization from the corresponding α-haloalkylamides XIXd and XIXe. The configurational analysis of azetidin-2-ones was accomplished on the basis of the existence of cross-ring coupling between N–CH_3 and C_3–H in their NMR spectra (see Experimental section), the supposition being made that the N–CH_3 group lies on the opposite side of the β-lactam ring to the C_4–C_6H_5 group.[8]

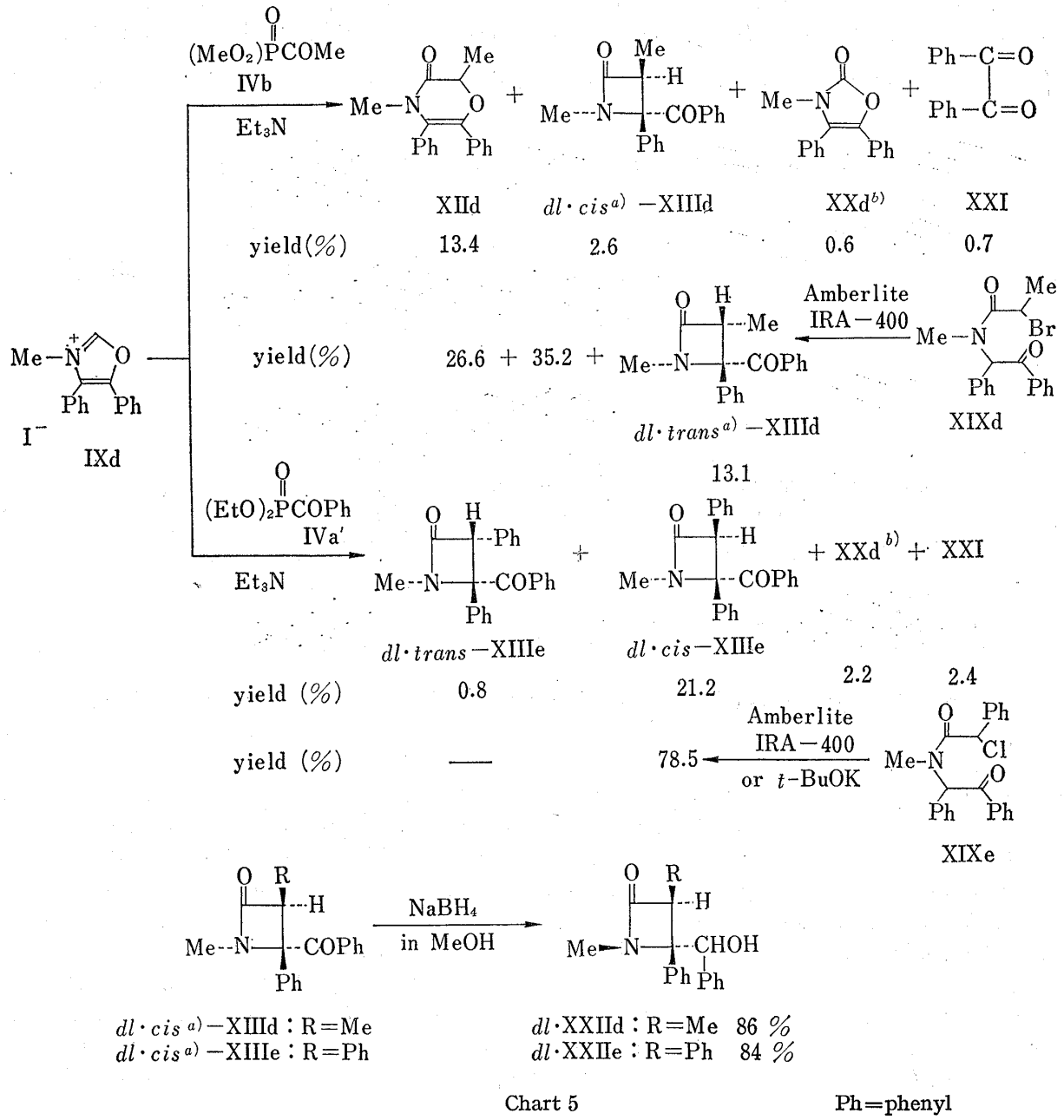


Chart 5 Ph=phenyl

a) configuration with respect to N-Me and C_3-H.
b) R. Gompper, *Chem. Ber.*, **89**, 1748 (1956); R. Gompper and H. Herlinger, *ibid.*, **89**, 2816 (1956).

$NaBH_4$ reductions of *cis*-XIIId and *cis*-XIIIe afforded the corresponding alcohols *dl*·XXIId and *dl*·XXIIe in 86% and 84% yield, respectively, which provided additional support for the presence of a ketonic carbonyl function in both compounds. On the basis of to was newly observed the cross-ring coupling (*dl*·XXIId: J=0.7 Hz, *dl*·XXIIe: J=0.8 Hz) between N–CH_3 and C_3–H in the NMR spectra of both hydrogenated products, it was found that hydrogenation proceeded with inversion of configuration of the N–CH_3 group.

Reaction Mechanism

The mechanism of the present reactions may be considered in comparison with the reaction behavior of the thiazolium salt described in the previous paper,[3] as shown in Chart 6. First, the C_2-carbanion of the oxazolium ylide A produced by treatment of salt IX with triethylamine in analogy with thiazolium ylide,[3] makes a nucleophilic attack on the carbonyl

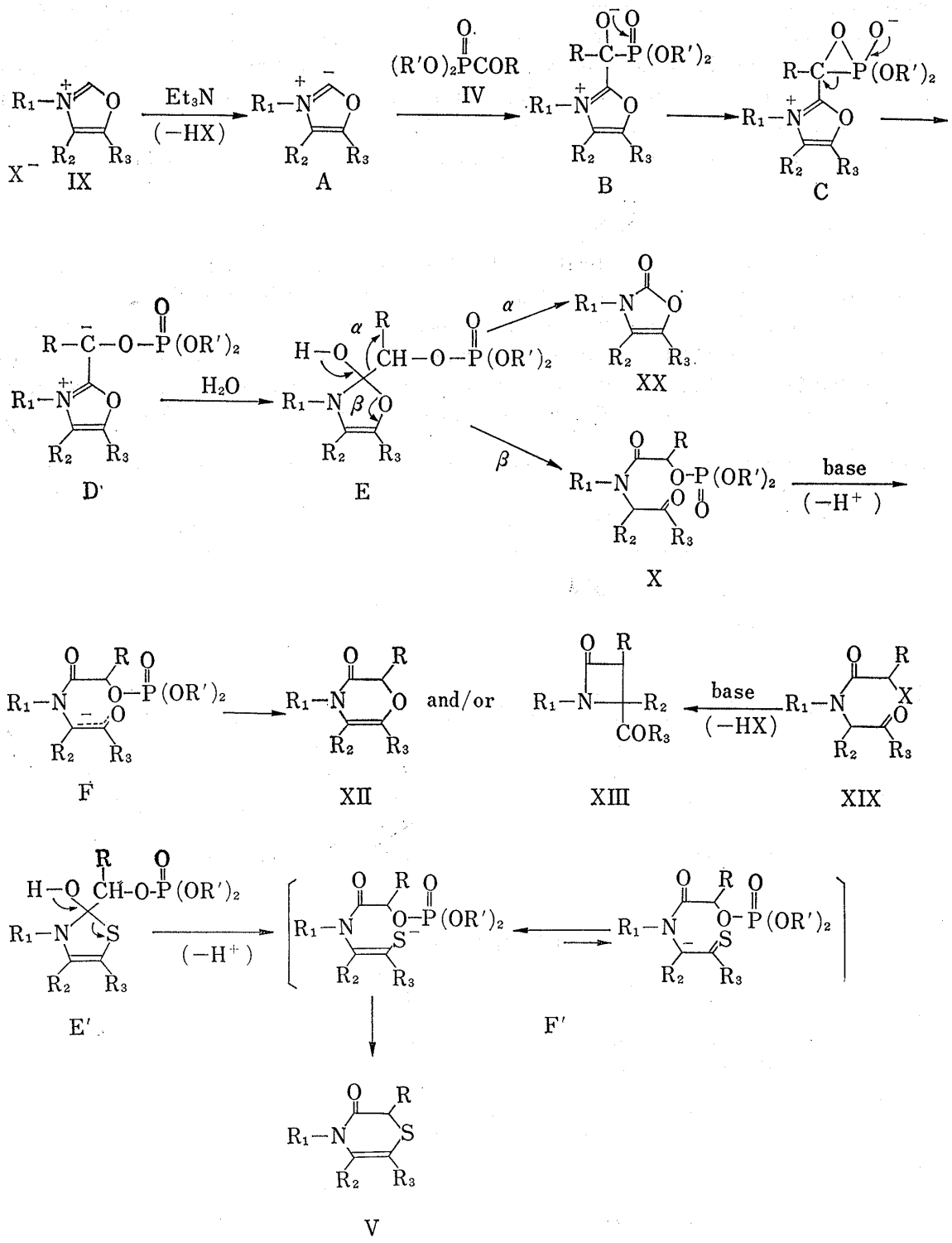


Chart 6

carbon of phosphonate IV, intramolecular rearrangement[11] follows to give betaine D, then addition of H_2O to D gives oxazoline E. Here, α-type bond fission in E leads to oxazol-2-one XX as a by-product, whereas β-type bond fission gives intermediate X. Subsequently, the ambident ion F generated by deprotonation of X with base cyclizes *via* its oxygen anion (*i.e.*,

11) L.A.R. Hall, C.W. Stephens, and J.J. Drysdale, *J. Am. Chem. Soc.*, **79**, 1768 (1957); Y. Okamoto, T. Nitta, and H. Sakurai, *Kogyo Kagaku Zasshi* (*J. Chem. Soc. Japan, Ind. Chem. Sect.*), **71**, 187 (1968).

enol form) to afford 1,4-oxazin-3-one XII, and *via* its carbanion (*i.e.*, keto form) to produce azetidin-2-one XIII. Such a pathway involving the transient intermediate F is supported by the fact that α-haloalkylamides XIX also give XII and XIII upon alkaline treatment.

On the other hand, reaction with the thiazolium salt gave 1,4-thiazin-3-one V as exclusive product[3] both because the equilibrium of the ambident ion F′, corresponding to the above F, shifts to the enthiolate form, and because the nucleophilicity of sulfur is higher than that of oxygen.

Substituent Effects

Several of the above results indicate that substituents in IX and IV strongly affect the reaction orientation, *i.e.*, direction of cyclization of the transient intermediate F. To obtain more detailed information on this, we next examined several different combination reactions between oxazolium salts (IX) and dialkyl acylphosphonates (IV). These results are summarized in Table III and IV. Using the reaction with thiamine as a model, we have already shown that alkyl substituents (R′) of dialkyl acylphosphonates (IV) do not affect the reactivity

Product Distributions in Reactions of Oxazolium Salts (IX) and Dialkyl Acylphosphonates (IV)

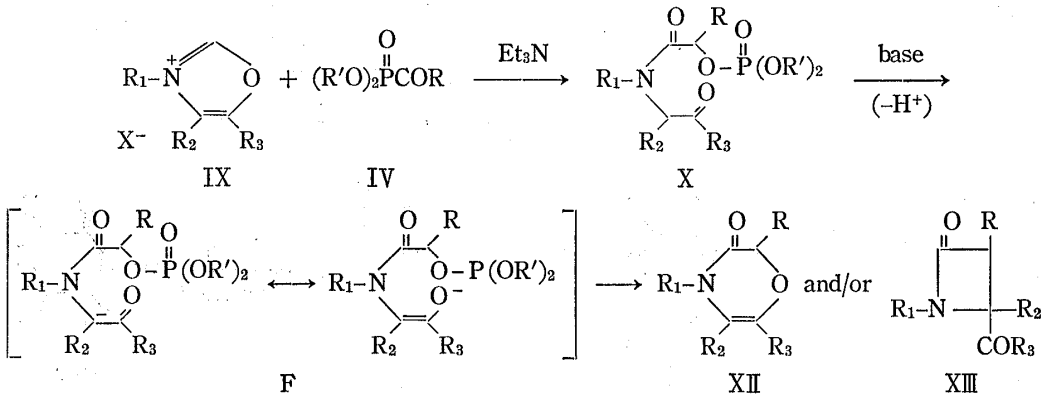


Table III. (Effects of Substituents on the Oxazolium Ring)

IVa	$(MeO)_2P(O)COPh$						
IX	R_1–N⁺ O, Cl^- Ph		Me–N⁺ O, I^- R_2 Ph			Me–N⁺ O, I^- Ph R_3	
	R_1=$PhCH_2$	R_1=Me	R_2=Me	R_2=H	R_2=Ph	R_3=Me	R_3=Ph
(%)[a]							
XII	25.6	18.1	0.5	18.1	—	—	—
XIII	14.2	10.3	11.8	10.3	22.0	15.7	22.0

Table IV. (Effects of Acyl Substituents of Phosphonates IV)

IX	$PhCH_2$–N⁺ O, Cl^- Ph			Me–N⁺ O, I^- Ph Ph			Me–N⁺ O, I^- Me Ph			Me–N⁺ O, I^- Ph Me		
IV (R)	Me	CH_2Ph	Ph	Me	CH_2Ph	Ph	Me	CH_2Ph	Ph	Me	CH_2Ph	Ph
(%)[a]												
XII	5.0	7.5	25.6	13.4	5.4	—	13.0	17.1	0.5	3.7	1.2	—
XIII	—	—	14.2	2.6	—	21.9	—	—	11.8	0.5	—	15.7

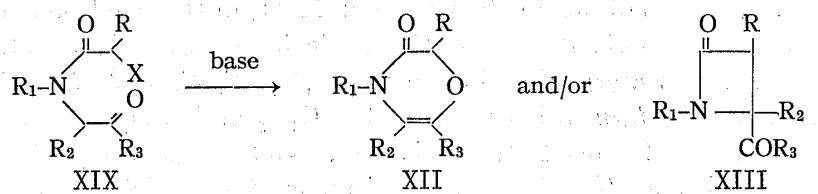
a) yields after preparative thin-layer chromatography on SiO_2($CHCl_3$) or Al_2O_3(ether)
Ph=phenyl

or the yield of product.[12] In addition, we believe that the low yields of products in Table III and IV are attributable mainly to the instability of the oxazolium ylide A and betaine D (see Chart 6) in the step IX→X, because the yield of cyclization of the isolated intermediate Xa to XIIa and XIIIa was comparable to that (see Table V shown below) of synthesis by an alternative route from α-haloalkylamide XIXa. Therefore, we can consider that in a discussion of the orientation of the present reaction comparison with the results in Table V is permissible.

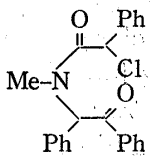
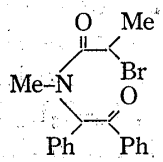
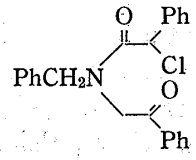
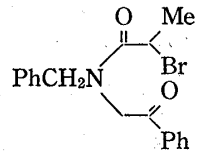
We first investigated the effects of substituents on the oxazolium ring using dimethyl benzoylphosphonate (IVa) (Table III). No effect of an N-substituent (R_1) such as a $C_6H_5CH_2$ or CH_3 group on product distribution was observed, though the yields of product from the CH_3 compound were less than those from the $C_6H_5CH_2$ compound, either because of stability of the reactive intermediate (betaine) D (see Chart 6) or because of the ease in crystallization of the product. The effect of the C_4-substituent (R_2), however, was remarkable; the C_6H_5 compound gave azetidin-2-one XIII as sole product, and the CH_3 compound gave the 1,4-oxazin-3-one XII in only 0.5% yield. These results can be explained as follows. In both case, the planarity of the $R_2 \cdot C=C \cdot R_3$ bond in the enol form of anion F, which is required for the formation of 1,4-oxazin-3-one XII, is hindered by mutual repulsion between the neighboring-groups, (*i.e.*, R_2 and R_3), and in the case of $R_2=C_6H_5$, in particular, a conjugative effect is also added to the steric effect. Consequently, the ambident anion F is exclusively or predominantly cyclized *via* the carbanion, *i.e.* by the keto-form, giving azetidin-2-one XIII. When $R_2=H$, on the other hand, the ratio in the formation of XII and XIII is 1.8: 1 on account of there being none of the above type of steric interaction. In the present consideration, of course, geometrical isomerism with respect to nitrogen and oxygen atoms in the enolate form of the anion F is a factor which cannot be ignored. No difference was observed in the substituent effects of the C_6H_5 and CH_3 groups at the C_5-position of IX.

Next we studied the effects of acyl substituents of phosphonates IV, *i.e.*, the R group in intermediate X. As can be seen in Table IV, the predominant product when the substituent $R=CH_3$ or $C_6H_5CH_2$ is 1,4-oxazin-3-one XII, while when $R=C_6H_5$ it is azetidin-2-one XIII, with all the oxazolium salts IX except one. These effects of R substituents can be considered as follows: In the transition state (*i.e.*, in ambident ion F), activation of carbon atom attached to the R group in F is weaker when the R group is CH_3 or $C_6H_5CH_2$ than when it is C_6H_5, consequently, in the former compounds bond formation of the carbon atom with the oxygen atom is favored energetically and sterically, and 1,4-oxazin-3-one XII is formed exclusively or predominantly. With C_2,C_4-unsubstituted oxazolium salts, a predominance

Table V. Product Distributions from Cyclization Reactions of α-Haloalkylamides (XIX)



XIX XII XIII

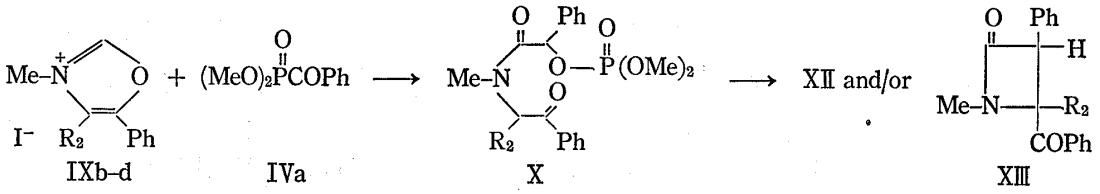
Amides (XIX) / Products (%)				
XII	—	26.6	29.1	72.4
XIII	78.5	48.3	13.3	—

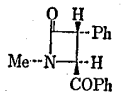
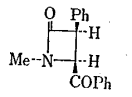
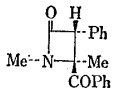
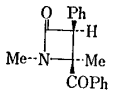
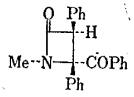
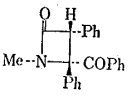
12) A. Takamizawa, Y. Sato, and H. Sato, *Chem. Pharm. Bull.* (Tokyo), **15**, 1183 (1967).

of 1,4-oxazin-3-one XII accompanied by smaller amounts of azetidin-2-one XIII was observed even when the R substituent was a C_6H_5 group, this being explainable in terms of the steric consideration described above.

Results supporting such an interpretation of the effects of substituents on the reactivity were obtained from the cyclization of α-haloalkylamides XIX to XII and/or XIII (Table V). When R_2=H, and R=CH_3 in XIX, XII was produced exclusively; but when the R substituent was a C_6H_5 group, the major product XII was accompanied by XIII. With XIX (R_2=C_6H_5, and R=C_6H_5) only XIII was produced; but XII was newly formed in 26.6% yield together with 48.3% yield of XIII when R was CH_3. The results suggest, moreover, that a C_6H_5 group as R_2 in XIX acts on the product distribution both sterically and electronically. No difference was seen between the effects of chlorine and bromine atoms in XIX on the product distribution. These product distributions were roughly consistent with those obtained from the corresponding compound IX and IV.

Table VI. Stereoisomeric Ratios of One of the Products, XIII, in the Reactions of Oxazolium Salts IXb-d with IVa



R_2	Cyclization with *trans*-orientation of Ph and COPh groups in X			Cyclization with *cis*-orientation of Ph and COPh groups in X		
H	*dl*		7.6%	*dl*		2.7%
Me	*dl*		6.2%	*dl*		5.6%
Ph	*dl*		21.1%	*dl*		0.8%

Ph=phenyl

The stereoisomeric ratios of one of the products, XIII, in the reactions of IXb, IXc, and IXd with IVa gave further indication that the steric factor strongly affects the reactivity (Table VI). Thus the less sterically hindered C_3–C_6H_5, C_4–C_6H_5CO-*trans*-isomer resulted from the cyclization with a *trans*-orientation of the C_6H_5 and C_6H_5CO groups in the intermediate X was formed in preference to the *cis*-isomer. In the case of R_2=C_6H_5, in particular, the proportion of *trans*-isomer (*i.e.*, C_6H_5, C_6H_5-*cis*) was 96%, which was comparable to the proportion of 100% obtained by ring closure of the corresponding α-haloalkylamide XIXe (see Chart 5), suggesting that a benzene ring-benzene ring charge-transfer interaction[13] in the transition state presumably serves as an effective driving force in both stereoselective reactions. With R_2=CH_3 the ratio of C_3–C_6H_5, C_4–C_6H_5CO-*trans*-isomer to the *cis*-isomer was 1.1: 1, suggesting that the steric repulsion between C_6H_5 and CH_3 groups is about the same as that between C_6H_5 and C_6H_5CO groups.

13) L.J. Andrews and R.M. Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, Inc., San Francisco, California, 1964; N. Tokura (eds.), "Denka'idosakutai," Kagakuzokan No. 49, Kagakudozin, Kyoto, 1971.

From these results of studies on the substituent effects, it is concluded that since the reaction is a competitive reaction between carbon and oxygen atoms in the intermediate X, its direction is dependent on the steric and electronic effects of substituents of IX and IV. The effects elucidated here make possible prediction of the reaction direction.

Reactions of 3-(2-Methyl-4-amino-5-pyrimidinyl)methyl-4,5-diethyloxazolium Bromide Hydrobromide (IXf) with Dialkyl Acylphosphonates (IV)

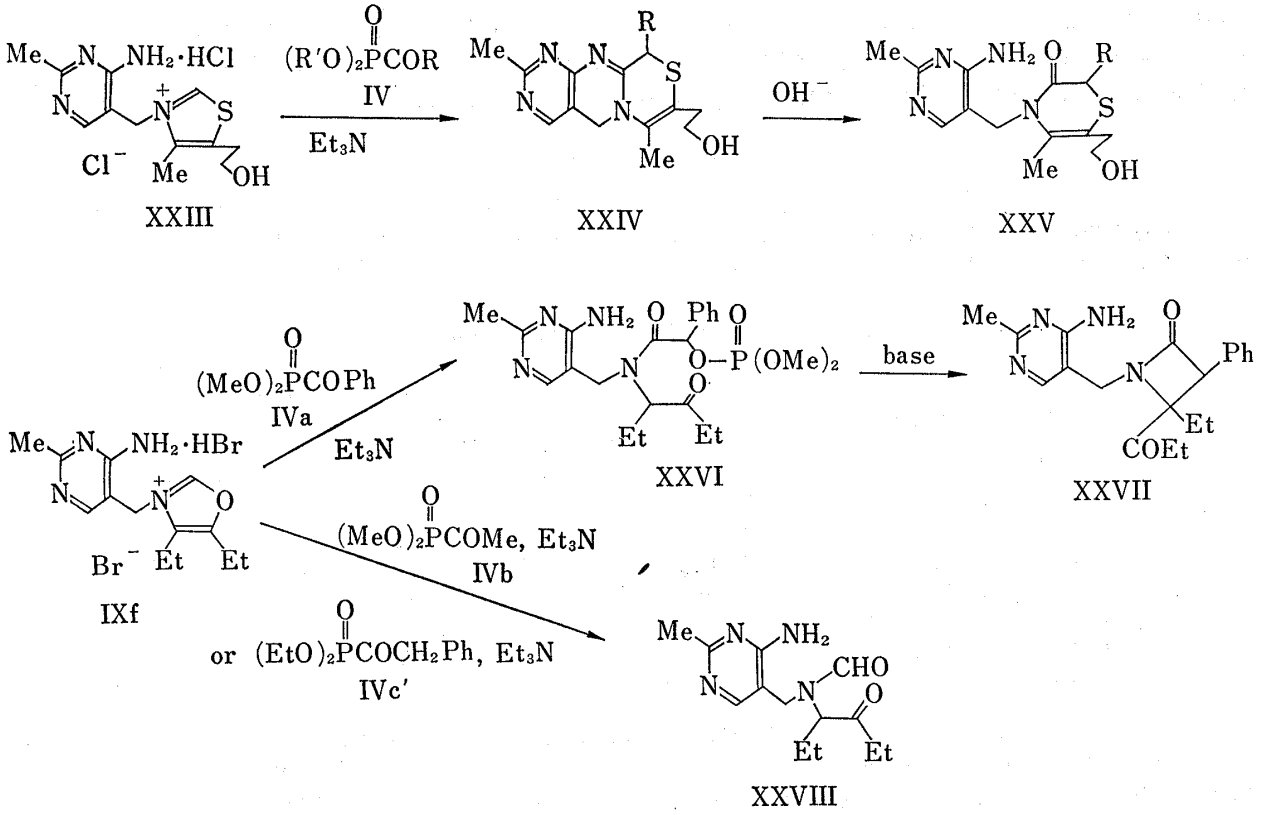


Chart 7 Ph=phenyl

In connection with the previously reported reactions of thiamine (XXIII) with dialkyl acylphosphonates (IV) to produce 2-alkyl-4-(2-methyl-4-amino-5-pyrimidinyl)methyl-5-methyl-6-(2-hydroxyethyl)-2,3-dihydro-4H-1,4-thiazin-3-ones (XXV) *via* 1-alkyl-3-(2-hydroxyethyl)-4,9-dimethyl-1,6-dihydropyrimido-[4',5': 4,5]pyrimido[2,1-*c*]-1,4-thiazines (XXIV),[14] we have now studied the reactions of 3-(2-methyl-4-amino-5-pyrimidinyl)methyl-4,5-diethyloxazolium bromide hydrobromide (IXf) as an O-heterothiamine analogue with phosphonates IV.

When the reaction of IXf with dimethyl benzoylphosphonate (IVa) was carried out carefully at −60° in an argon atmosphere, colorless crystals, mp 243—244°, were obtained. This product was shown to have the expected structure of a 1:1 adduct (free base) XXVI of IXf and IVa on the basis of the analytical and spectral data ($C_{22}H_{31}O_6N_4P$; UV λ_{max}^{EtOH} mμ: 253; IR ν_{max}^{Nujol} cm^{-1}: 1724, 1654, 1226, 1059, and 1043). Treatment of XXVI with Amberlite IRA-400 in methanol or NaOH in aq. ethanol gave azetidin-2-one derivative XXVII, whose formation was expected from the results of studies on the substituent effects described above, as two stereoisomers (mp 207—210°; $C_{20}H_{24}O_2N_4$; UV λ_{max}^{EtOH} mμ: 234, 275; IR $\nu_{max}^{CHCl_3}$ cm^{-1}:

14) A. Takamizawa, Y. Hamashima, Y. Sato, H. Sato, S. Tanaka, H. Ito, and Y. Mori, *J. Org. Chem.*, **31**, 2951 (1966); A. Takamizawa, Y. Hamashima, Y. Sato, and H. Sato, *Chem. Pharm. Bull.* (Tokyo), **15**, 1178 (1967).

1743, 1716 and mp 138—139°; $C_{20}H_{24}O_2N_4$; UV λ_{max}^{EtOH} mμ: 235^{sh}, 277; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1741, 1718) arising from difference of configuration of the substituents at the C_3 and C_4 positions on the azetidine ring.

The reaction of IXf with dimethyl acetylphosphonate (IVb) or phenylacetylphosphonate (IVc') was not successful, only N-[(2-methyl-4-amino-5-pyrimidinyl)methyl]-N-[1-ethyl-2-oxobutyl]formamide (XXVIII) being obtained. This may be considered to be attributable to the lower reactivity of IVb and IVc' than IVa, or to instability of the reaction intermediates, though the reason is not clearly understood. It is of interest that Tomita, *et al.*[15] have reported that an O-heterothiamine undergoes ring opening through ready hydrolysis to yield N-[(2-methyl-4-amino-5-pyrimidinyl)methyl]-N-[1-methyl-2-oxo-4-hydroxybutyl]formamide (*i.e.*, desthiothiamine) in alkaline medium and even in neutral medium.

Experimental[16]

General Procedure for Preparation of Oxazolium Salts IXa—f——An excess of alkyl halide was allowed to react with the oxazole (VIII). The results obtained are summarized in Tables I and VII.

TABLE VII. Analytical Data for Oxazolium Salts IXa-f

Compd. No.	Formula	Calcd. (%)			Found (%)		
		C	H	N	C	H	N
IXa	$C_{16}H_{14}ONCl$	70.70	5.19	5.15	70.16	5.53	5.06
IXb	$C_{10}H_{10}ONI$	41.83	3.48	4.88	42.13	3.57	4.84
IXc	$C_{11}H_{12}ONI$	43.89	4.02	4.65	43.99	4.23	4.73
IXd	$C_{16}H_{14}ONI$	52.89	3.89	3.86	53.16	3.95	3.53
IXe	$C_{11}H_{12}ONI$	43.89	4.02	4.65	44.13	3.98	4.52
IXf	$C_{13}H_{20}ON_4Br_2$	38.25	4.94	13.73	38.14	5.17	13.64

Reaction of Oxazolium Salts IXa with IVa——To a stirred mixture of IXa (1.0 g) and IVa (0.8 g) in DMF (30 ml), Et_3N (dried over Na wire, 1.2 g) was added dropwise at −53——56° over 40 min in an atmosphere of dry argon. The mixture was then stirred for 2 hr at −55——60°, for 15 hr at −60——19°, then for 7 hr at −19——11°. DMF was removed *in vacuo* below 46° and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 5% $NaHCO_3$ and H_2O successively, dried over Na_2SO_4, and evaporated. The oily residue crystallized from ether to give the product (1.27 g, 74%), mp 128—131°. Recrystallization from acetone gave colorless prisms, mp 135—140°. *Anal.* Calcd. for $C_{25}H_{26}O_6NP$ (Xa): C, 64.22; H, 5.61; N, 3.00; P, 6.63. Found: C, 64.43; H, 5.75; N, 2.86; P, 6.54.

$NaBH_4$ Reduction of Xa——To a solution of Xa (405 mg) in MeOH (20 ml) was added $NaBH_4$ (200 mg) under ice cooling and the mixture was stirred for 30 min at 2—5° and for 2 hr at room temperatures. MeOH was removed by evaporation under reduced pressure to give a colorless residue which was extracted with $CHCl_3$. The combined $CHCl_3$ extract was washed with dil. AcOH and H_2O successively, dried over Na_2SO_4, and evaporated. The oily residue crystallized from ether to give colorless crystals (XIa, 212 mg, 52.2%), mp 135—140°. Recrystallization from ether–AcOEt gave colorless prisms, mp 148—150°. *Anal.* Calcd. for $C_{25}H_{28}O_6NP$ (XIa): C, 63.95; H, 6.02; N, 2.99; P, 6.60; mol. wt., 469.487. Found: C, 64.34; H, 6.07; N, 3.04; P, 5.89; mol. wt. ($CHCl_3$), 467.3. From the mother liquor of the above crude crystals, colorless crystals (112 mg, 27.6%) of mp 125—127° were obtained on standing under ice cooling. Recrystallization from ether–AcOEt gave colorless prisms, mp 125—128°. *Anal.* Calcd. for $C_{25}H_{28}O_6NP$ (XIb): C, 63.95; H, 6.02; N, 2.99; P, 6.60; mol. wt., 469.487. Found: C, 64.24; H, 6.18; N, 3.05; P, 5.76; mol. wt. ($CHCl_3$), 466.4.

15) I. Tomita, M. Noda, and T. Ozawa, *Chem. Pharm. Bull.* (Tokyo), **16**, 1858 (1968).

16) All melting points are uncorrected. All NMR spectra were taken with a Varian A-60 spectrometer in $CDCl_3$ or d_6-DMSO containing TMS as internal reference. Chemical shifts are expressed in τ values and coupling constants in Hz. Multiplicities of signals are represented as a s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), b (broad), and m (multiplet). Mass spectra were taken with a Hitachi RMU-6E mass spectrometer using a direct inlet system with the ionizing energy at 70 eV and the ionizing current at 80 μA.

Treatment of Xa with Amberlite IRA-400——Amberlite IRA-400 (chloride form, 50 g) was converted to its hydroxyl form by stirring for 45 min with excess 10% aqueous NaOH. The resin was washed with water until the washings were neutral to pH paper, then it was washed thoroughly with MeOH to remove as much water as possible. The resin was suspended in 130 ml MeOH and stirred. Xa (1000 mg) was added and the mixture was stirred overnight at room temperatures, then filtered. The resin was washed several times with MeOH. MeOH was removed *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and evaporated. The oily residue was submitted to preparative thin-layer chromatography (PLC) on Kieselgel GF_{254} nach Stahl (E. Merck) and developed with $CHCl_3$. From the fraction with the greater *Rf* value, colorless crystals (XIIa, 253 mg, 34.6%), mp 106—109°, were obtained by extraction with MeOH. *Anal.* Calcd. for $C_{23}H_{19}O_2N$: C, 80.91; H, 5.61; N, 4.10; O, 9.37. Found: C, 80.88; H, 5.31; N, 4.04; O, 9.60. The fraction with the lower *Rf* value, after extraction with MeOH, was rechromatographed on Al_2O_3 GF_{254} (E. Merck) and developed with ether. The higher position band gave colorless crystals (*dl*·*trans*-XIIIa, 102 mg, 14.0%), mp 111—113°. *Anal.* Calcd. for $C_{23}H_{19}O_2N$: C, 80.91; H, 5.61; O, 9.37; N, 4.10. Found: C, 80.92; H, 5.35; O, 9.46; N, 4.08. The lower position band gave colorless crystals (*dl*·*cis*-XIIIa, 38 mg, 5.2%), mp 186—188°. *Anal.* Calcd. for $C_{23}H_{19}O_2N$: C, 80.91; H, 5.61; N, 4.10. Found: C, 81.15; H, 5.51; N, 4.07.

Preparation of 2,4-Dinitrophenylhydrazone (XIVa) of *dl*·*cis*-XIIIa——To a solution of *dl*·*cis*-XIIIa (50 mg) in EtOH, a suitable amount of a sulfuric acidic solution of 2,4-dinitrophenylhydrazine was added. The mixture was allowed to stand at room temperature for 2 hr, then water was added and the crystals (49 mg) which deposited were collected. Recrystallization from EtOH gave yellow crystals, mp 199—200°. *Anal.* Calcd. for $C_{29}H_{23}O_5N_5$ (XIVa): C, 66.78; H, 4.45; N, 13.43. Found: C, 66.73; H, 4.16; N, 13.68.

Treatment of α-Haloalkylamide XIXa with Amberlite IRA-400——To a solution of XIXa (purity: 65%, 1000 mg) in MeOH (130 ml) was added Amberlite IRA-400 (50 g) which had been converted to the OH form by aq. NaOH treatment. After being stirred overnight at room temperature, the reaction mixture was treated according to the procedure (PLC separation) used for Xa, to give XIIa (29.1%), *dl*·*trans*-XIIIa (9.2%), and *dl*·*cis*-XIIIa (4.1%). These products were shown to be identical with authentic samples obtained above by IR, UV, and TLC comparisons.

Reaction of Oxazolium Salts IXb with IVa——A mixture of IXb (1.0 g), IVa (0.8 g), DMF (30 ml), and Et_3N (0.7 g) was treated according to the procedure described for the reaction of IXa with IVa. The crude oily product was submitted to Al_2O_3 chromatography. Elution with ether removed impurities and subsequent elution with AcOEt gave a colorless oil (Xb, 0.425 g, 31.2%). *Anal.* Calcd. for $C_{19}H_{22}O_6NP$: C, 58.30; H, 5.67; N, 3.58; P, 7.92. Found: C, 58.03; H, 5.90; N, 3.75; P, 7.61. NMR (τ, in $CDCl_3$): 7.03 (3H, s, CH_3), 6.41 (3H, d, J_{PH}=11.3 Hz, OCH_3), 6.16 (3H, d, J_{PH}=11.3 Hz, OCH_3), 5.36 and 4.96 (2H, AB-quartet, J=17.1 Hz, N-CH_2), 3.82 (1H, d, J_{PH}=8.1 Hz, CH-O-P(O)), 2.7—1.9 (10H, m, aromatic-H). IR ν_{max}^{Film} cm^{-1}: 1702, 1670, 1278, 1041, and 1020.

Treatment of Xb with Amberlite IRA-400——Xb was treated with Amberlite IRA-400 (OH form) according to the procedure outlined for Xa, to give XIIb, *dl*·*trans*-XIIIb, and *dl*·*cis*-XIIIb. Physical constants and yields of these products are listed in Table VIII.

Table VIII. Physical Constants and Yields of XIIb, *dl*·*trans*-XIIIb, and *dl*·*cis*-XIIIb

	XIIb	*dl trans*-XIIIb	*dl cis*-XIIIb
mp (°C)	130—134	91—94	142—144
UV λ_{max}^{EtOH} mμ	309	248.5	251
IR $\nu_{C=O}^{CHCl_3}$ cm^{-1}	1680	1762, 1694	1758, 1696
NMR ($CDCl_3$, τ, Hz)	C_2-H, 4.30 (s)	C_3-H, 5.85 (d-d, J=2.7, J=0.7)	C_3-H, 5.15 (d-d, J=6.0, J=0.7)
	C_5-H, 3.84 (s)	C_4-H, 5.11 (d, J=2.7)	C_4-H, 4.68 (d, J=6.0)
	N-Me, 6.78 (s)	N-Me, 6.92(d, J=0.7)	N-Me, 6.88 (d, J=0.7)
Yield[a] (%) from IXb	18.1	7.6	2.7

b) yields after preparative thin-layer chromatography on SiO_2($CHCl_3$) and Al_2O_3(ether)

Reaction of Oxazolium Salt IXc with IVa——To a mixture of IXc (3.0 g) and IVa (2.2 g) in DMF (30 ml), Et_3N (2.2 g) was added dropwise at −50——55° during 1 hr in an atmosphere of dry argon, and the mixture was stirred for 5.5 hr at −60——40°. The mixture was left to stand overnight at −60——10°, DMF was removed *in vacuo* below 45°, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over Na_2SO_4, and evaporated. The oily residue was treated with Amberlite IRA-400 (OH form) in MeOH and submitted to PLC on Al_2O_3 (ether and $CHCl_3$). The results are summarized in Table II and the elemental analyses are listed in Table IX.

Reactions of Oxazolium Salt IXd with Dialkyl Acylphosphonates (IVb and IVa')——General Procedure: To a mixture of IXd (8 mmoles), IV (8 mmoles), and DMF (25 ml), Et_3N (16 mmoles) was added dropwise

Table IX. Analytical Data for the Products

Compd. No.	Formula	Calcd. (%)			Found (%)		
		C	H	N	C	H	N
XIIc	$C_{18}H_{17}O_2N$	77.39	6.13	5.01	77.43	5.91	4.94
dl·*trans*-XIIIc	$C_{18}H_{17}O_2N$	77.39	6.13	5.01	77.62	6.15	5.05
dl·*cis*-XIIIc	$C_{18}H_{17}O_2N$	77.39	6.13	5.01	77.16	5.93	5.22
XXc	$C_{11}H_{11}O_2N$	69.82	5.86	7.40	70.09	5.89	7.31

Table X. Physical Constants of XIId, *dl*·*cis*-XIIId, and *dl*·*trans*-XIIId

	XIId	*dl*·*cis*-XIIId	*dl*·*trans*-XIIId
mp (°C)	98—102	141—145	77
UV λ_{max}^{EtOH} mμ (log ε)	301 (3.91)	253 (4.09)	252 (4.03)
IR $\nu_{max}^{CHCl_3}$ cm^{-1}	1675	1751, 1687	1747, 1684
NMR ($CDCl_3$, τ, Hz)	N–Me, 7.14 (s)	N–Me, 7.22 (s)	N–Me, 7.15 (d, J=0.8)
	C_2–Me, 8.37 (d, J=6.8)	C_3–Me, 8.33 (d, J=7.5)	C_3–Me, 9.00 (d,J=7.5)
	C_2–H, 5.37 (q, J=6.8)	C_3–H, 5.83 (q, J=7.5)	C_3–H, 5.99 (d-q, J=0.8, J=7.5)

Table XI. Physical Constants of *dl*·*trans*-XIIIe and *dl*·*cis*-XIIIe

	dl·*trans*-XIIIe	*dl*·*cis*-XIIIe
mp (°C)	oil	178—180
UV λ_{max}^{EtOH} mμ	252.5	254.5
IR $\nu_{max}^{CHCl_3}$ cm^{-1}	1753, 1683	1755, 1686
NMR ($CDCl_3$, τ, Hz)	N–Me, 7.10 (d, J=0.8)	N–Me, 7.08 (s)
	C_3–H, 4.466 (q, J=0.8)	C_3–H, 4.82 (s)

at −50——60° during *ca.* 30 min in an atmosphere of argon, and the mixture was stirred for 5—6 hr at *ca.* −50°. After being left overnight at −50——60°, the reaction mixture was treated as described above. The results are summarized in Chart 5, and Tables X and XI.

$NaBH_4$ Reduction of *dl*·*cis*-XIIId and *dl*·*cis*-XIIIe——To a solution of *dl*·*cis*-XIIId or *dl*·*cis*-XIIIe (one part by weight) in MeOH, $NaBH_4$ (one part by weight) was added under ice cooling with vigorous stirring. The reaction mixture was stirred for 30 min below 5° and for 1 hr at room temperature. The mixture was left overnight at 25—30°, then MeOH was evaporated *in vacuo* to leave a colorless residue which was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over Na_2SO_4, and evaporated. The oily residue was crystallized from petroleum ether or ether. Recrystallization from ether–EtOH then gave XXIId or XXIIe as colorless crystals. Physical constants, yields, and elemental analyses of the products are listed in Table XII.

Reaction of 3-(2-Methyl-4-amino-5-pyimidinyl)methyl-4,5-diethyloxazolium Bromide Hydrobromide (IXf) with IVa——To a stirred mixture of IXf (7.35 mmoles) and IVa (7.47 mmoles) in dry DMF (25 ml), Et_3N (22.8 mmoles) was slowly added dropwise at −65——63° under dry argon atmosphere. The mixture was stirred for 5.5 hr at −60°, then left to stand overnight at −53——12°. DMF was removed *in vacuo* at 45°, and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over Na_2SO_4, and evaporated.

A part of the residue was subjected to PLC (SiO_2–acetone) to give colorless crystals, mp 243—244°. *Anal.* Calcd. for $C_{22}H_{31}O_6N_4P$ (XXVI): C, 55.22; H, 6.53; N, 11.71; P, 6.48. Found: C, 54.89; H, 6.79; N, 11.32; P, 5.56. The rest of the residue was dissolved in a mixture of 99% EtOH (10 g) and 10% NaOH (10 g) and refluxed for 30 min. The solution was concentrated and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and evaporated *in vacuo*. The residual oil was crystallized from ether to give colorless crystals (127 mg), mp 195—203°. Recrystallization from dil. EtOH gave colorless scales, mp 207—210°. *Anal.* Calcd. for $C_{20}H_{24}O_2N_4$ (XXVII): C, 68.16; H, 6.86; N, 15.90. Found: C, 68.38; H, 6.99; N, 15.81. The mother liquor of the above crude crystals (mp 195—203°) was subjected to PLC (SiO_2–acetone). The lower position band gave an additional XXVII (20 mg), mp 204—206°, while the higher position band gave colorless crystals (32 mg), mp 138—139°, which were assigned as a stereoisomer of XXVII obtained above. *Anal.* Calcd. for $C_{20}H_{24}O_2N_4$ (XXVII): C, 68.16; H, 6.86; N, 15.90. Found:

Table XII. Physical Constants, Yields, and Analytical Data of *dl*·XXIId and *dl*·XXIIe

	dl·XXIId	*dl*·XXIIe
mp (°C)	157—159	150—153
IR $\nu_{max}^{CHCl_3}$ cm^{-1}	3600, 1740	3594, 3560, 1747
Yield (%)	85.6	84.3

	Formula	Calcd. (%)			Found (%)		
		C	H	N	C	H	N
dl·XXIId	$C_{18}H_{19}O_2N$	76.84	6.81	4.98	76.64	6.53	5.28
dl·XXIIe	$C_{23}H_{21}O_2N$	80.44	6.16	4.08	80.17	6.13	3.96

C, 68.12; H, 6.58; N, 15.71. Yields of XXVII: the higher mp compound, 19.1%; the lower mp compound, 4.2%. Stereochemical studies on XXVII are now in progress.

Reaction of IXf with IVb (or IVc')——A mixture of IXf (7.35 mmoles), IVb (7.56 mmoles) [or IVc' (7.42 mmoles)], DMF (25 ml), and Et_3N (22.8 mmoles) was worked up according to the procedure described for the reaction of IXf with IVa. After evaporation of DMF *in vacuo* below 45° from the reaction mixture, the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 5% $NaHCO_3$ and H_2O successively, dried, and evaporated. The oily residue was treated with Amberlite IRA-400 (OH form) in MeOH and submitted to PLC on SiO_2 (acetone) to yield colorless crystals (yield, 10.0%), mp 143—148°. *Anal.* Calcd. for $C_{13}H_{20}O_2N_4$ (XXVIII): C, 59.07; H, 7.63; N, 21.20. Found: C, 58.84; H, 7.76; N, 20.93. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1726, 1655. Yield of XXVIII in the case of IVc', 32.2%.