[Chem. Pharm. Bull. 17(11)2201—2208(1969)] UDC 547.786.1.04

Isoxazoles. XX.[1] Base-induced Ring Cleavage Reactions of 2,3,4-Trisubstituted Isoxazolium Salts

Ikuo Adachi and Hideo Kanō

Shionogi Research Laboratory, Shionogi & Co., Ltd.[2]

(Received November 19, 1968)

Ring opening reactions with some bases were examined in the following quaternary salts: 2-ethyl-3,4-diphenylisoxazolium chloroferrate (V), and 2,4-dimethyl-3-phenyl-, 3,4-diphenyl-2-methyl- and 2-methyl-3-phenylisoxazolium perchlorate (IXa, b and c). Treatments of V and IX with sodium alcoholate in alcohol gave the corresponding alkyl cinnamates (VIIa—e). By the use of aqueous sodium hydroxide, V and IXb gave the respective cinnamic anhydrides (Xa and b) contrary to the report of Kohler, *et al.*, and IXa gave an unexpected product, 2,5-diphenyl-1,3,4-trimethylpyrrole (XIa) along with usual ring cleaved products, XIIa and XIIIa. Reactions of IXa, b with several amines gave β-keto acid amides (XIIc—h), the ketones (XIIIa, b) and the pyrrole (XIa) (only from IXa), respectively. Reactions of IXa with Grignard reagents gave 5-substituted Δ^3-isoxazolines (XIVa, b). Similar 5-amino-Δ^3-isoxazolines (XVa—c) were obtained by cautious treatment of IXa, b with piperidine or morpholine. Solvolysis of X, XIV and XV were also investigated, and a tentative mechanism for the formation of the various products are presented.

The 3- or 5-unsubstituted isoxazoles are unstable towards alkali and the ring opening with alkali is believed to proceed through initial abstraction of the C_3- or C_5-proton.[3] We have suggested a similar mechanism to explain the transformation of 3-phenyl-4-hydroxyalkylisoxazoles (I) into the lactones (II) in the foregoing paper.[1]

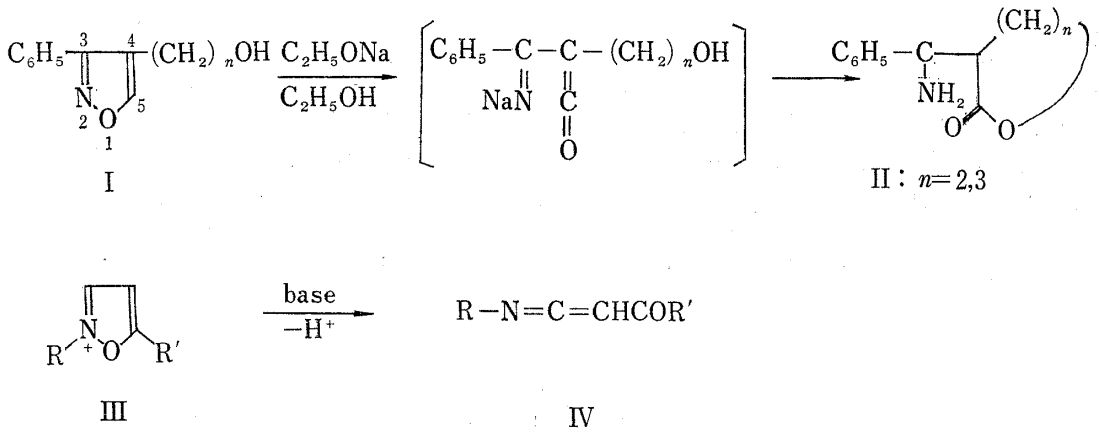


Chart 1

Quaternization of the nitrogen atom of the isoxazole nucleus makes the ring particularly susceptible towards nucleophilic attack and the mechanism of the quaternary salts of 3-unsubstituted isoxazoles (III) was first elucidated only in 1961 by Woodward and Olofson.[4] They

1) Part XIX: I. Adachi and H. Kanō, *Chem. Pharm. Bull.* (Tokyo), **16**, 117 (1968).
2) Location: *Fukushima-ku, Osaka.*
3) A. Quilico, "The Chemistry of Heterocyclic Compounds," Vol. 17, ed. by R.H. Wiley, Interscience Publishers, Inc., New York, N.Y., 1962, p. 44.
4) R.B. Woodward and R. Olofson, *J. Am. Chem. Soc.*, **83**, 1007 (1961).

succeeded to prove the presence of the β-ketoketenimine intermediate (IV) by use of infrared spectroscopy.

As to the quaternary salts of 5-unsubstituted series, there has been only a paper on the reaction of 3,4-diphenyl-2-ethylisoxazolium chloroferrate (V) with sodium hydroxide in benzene reported by Kohler, *et al.*[5] The authors assigned to the product obtained from V the bismolecular anhydride (VI) which gave the β-ethylaminocinnamate (VII) on methanolysis. Although they claimed that the anhydride can arise from initial addition of the hydroxy ion at C-5 of the ring, the structure of VI was not well founded.

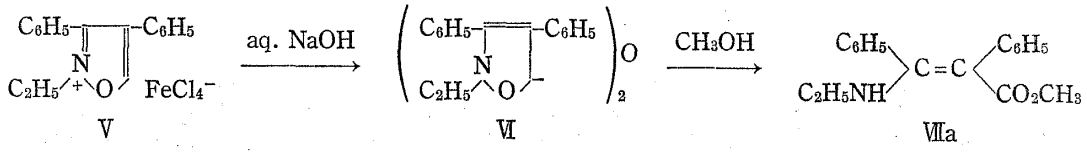


Chart 2

In relation to our foregoing work[1] and the question about the structure assignment of VI, this work was undertaken to reexamine the reactions of 2,3,4-trisubstituted isoxazolium salts (IX). Our syntheses of IX and V involved quaternization of the corresponding isoxazoles (VIII) which were obtained by use of 1,3-dipolar cycloaddition of benzonitrile oxide to the appropriate dipolarophiles (1-piperidino-1-propene, styryl acetate, ethyl vinyl ether).

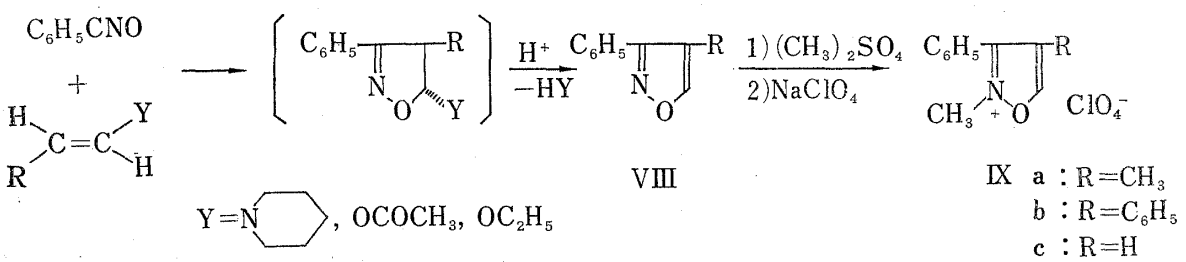


Chart 3

By the same procedure as described by Kohler, *et al.*[5] or by our improved procedure using a mixture of triethylamine, acetonitrile and water, V and IXb gave the products whose molecular formulas are in accord with the anhydride VI and its N-methyl analog, respectively. However, these products showed infrared (IR) bands attributable to NH (3210 and 3225 cm^{-1}, respectively) and their nuclear magnetic resonance (NMR) spectra also exhibited NH-proton peaks (τ 0.22 and τ 0.25, respectively). These spectral data spoke against the structure VI and its analog, and were consistent with the cinnamic anhydride derivatives (X). Methanolysis of the anhydrides Xa,b afforded the corresponding methyl β-alkylaminocinnamates (VIIa) and (VIIb).

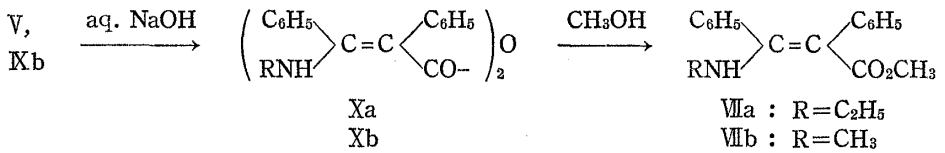


Chart 4

Treatment of IXa,b with sodium alcoholate in alcohol also gave the corresponding alkyl β-methylaminocinnamates (VIIc,d,e) quantitatively, which were hydrolized with sodium hydroxide in aqueous ethanol to afford the known β-ketoesters.[6] By the use of aqueous cold sodium hydroxide, the salt IXa gave an unexpected product of composition $C_{19}H_{19}N$

5) E.P. Kohler and A.R. Davis, *J. Am. Chem. Soc.*, **52**, 4520 (1930).

(XIa, mp 101—102°) in about 30% yield besides usual ring cleavage products (XIIa[7] and XIIIa). Treatment of IXa with methanolic ammonia gave XIa and $C_{18}H_{17}N$ (XIb, mp 142—143°) in 15.4% and 17.1% yield, respectively, along with the acid amide (XIIb).[8] The NMR spectra of XIa and XIb in $CDCl_3$ showed the signals of two C–CH_3 groups (at τ 7.97 for XIa and 7.79 for XIb, each as singlet), a N–CH_3 group for only XIa (at τ 6.70 as singlet), and two phenyl groups (at τ 2.67 as singlet for XIa and 2.60 as multiplet for XIb). The ultraviolet (UV) spectra of XIa and XIb in ethanol display maxima at 309 mμ (log ε 4.229) and 322 mμ (log ε 4.411), respectively, which were comparable to those of the known 1-methyl-2,5-diphenylpyrrole (307 mμ) and 2,5-diphenylpyrrole (325 mμ).[9] Based on these data the structures of 1,3,4-trimethyl- and 3,4-dimethyl-2,5-diphenylpyrroles (XIa and XIb) were assigned to $C_{19}H_{19}N$ and $C_{18}H_{17}N$, respectively. The structure assignment was confirmed by an unequivocal synthesis of XIa,b from 2,3-dibenzoylbutane with ammonia and methylamine.

Reactions of IXa, b, with several primary and secondary amines gave the corresponding β-keto acid amides (XIIc—h), the ketones (XIIIa, b) and the pyrrole XIa (only from IXa). The β-keto acid amides has arisen from hydrolysis of their β-methylamino derivatives (XII') on passage through alumina column. None of the pyrrole derivative could be detected in any nucleophilic cleavage reactions of IXb and IXc. This suggests that the methyl group at C-4 may play an important role for the pyrrole formation.

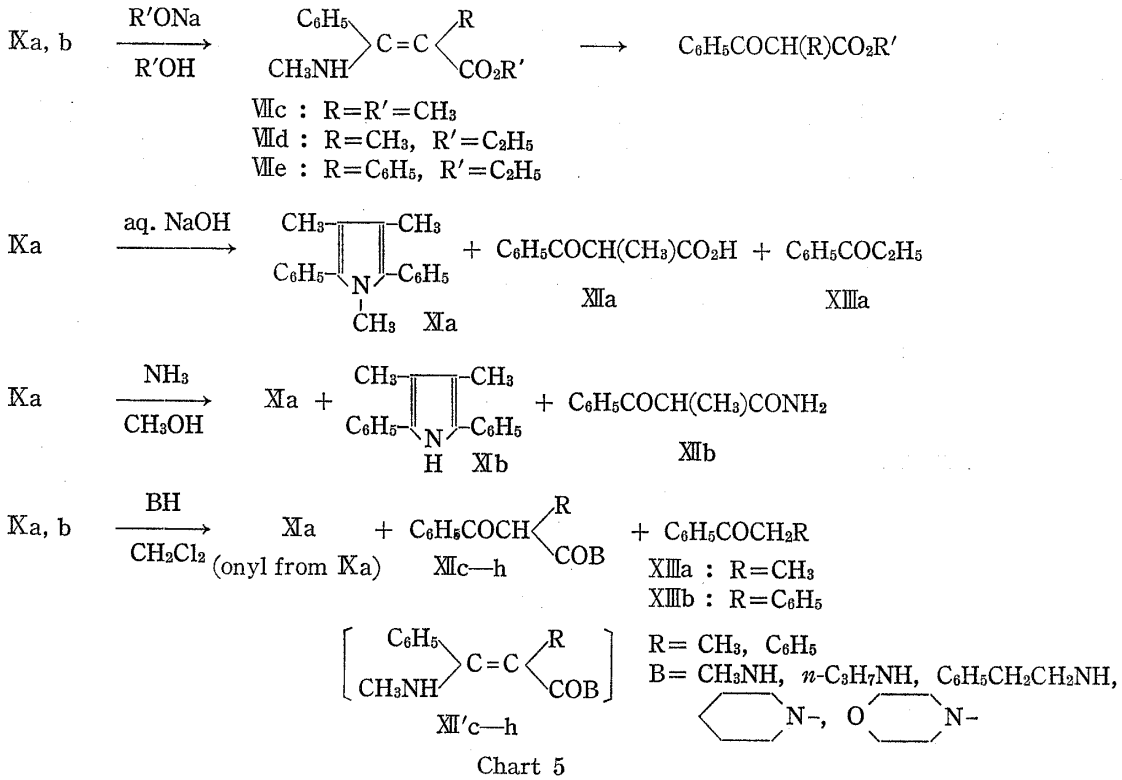


Chart 5

Formation of the products VII, XII and XIII from IX can be visualized as occurring from either initial addition of nucleophiles at C-5 (course a) or abstraction of the proton at C-5 (course b). Two abnormal products, the anhydride X and pyrrole XI, may arise from reactions involving the ketene intermediate though attempt to prove the presence of the ketene intermediate by infrared spectroscopy was unsuccessful.

6) W.H. Perkin and A. Calman, *J. Chem. Soc.*, **1886**, 156.
7) E. Hope and W.H. Perkin, *J. Chem. Soc.*, **1909**, 2045.
8) This compound was confirmed by an unequivocal synthesis from ethyl 2-benzoylpropionate with ammonia.
9) S.W. King, C.R. Bauer and R.E. Lutz, *J. Am. Chem. Soc.*, **73**, 2253 (1951).

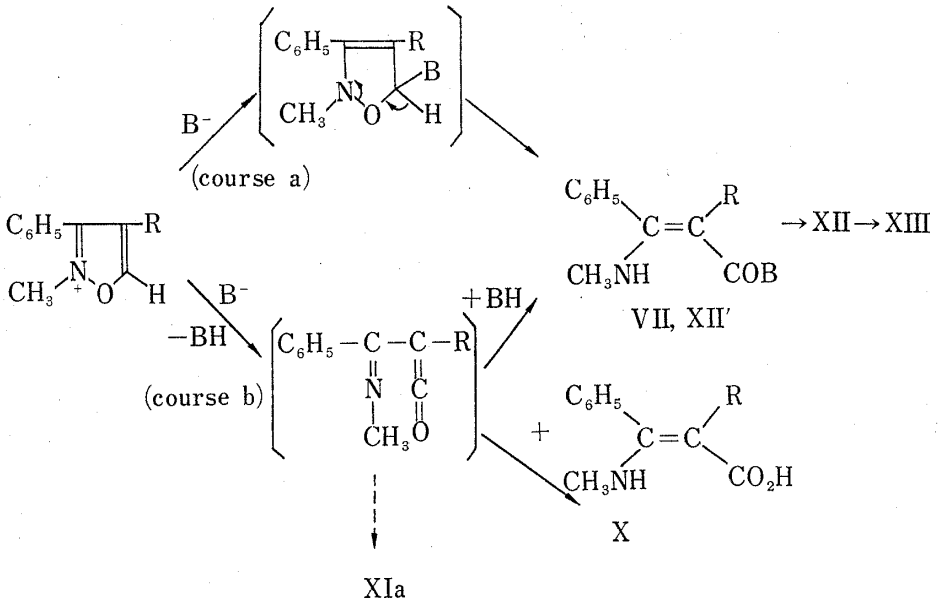


Chart 6

Although no decision between these possible pathway can reached from the present data, we succeeded to isolate some Δ^3-isoxazoline derivatives in the reactions of IX with nucleophiles. Treatment of IXa with Grignard reagents at low temperature gave 5-substituted Δ^3-isoxazolines (XIV). Similar 5-amino-Δ^3-isoxazolines (XV) were obtained quantitatively by the reaction of IXa, b with piperidine or morpholine at low temperature. The products reverted to

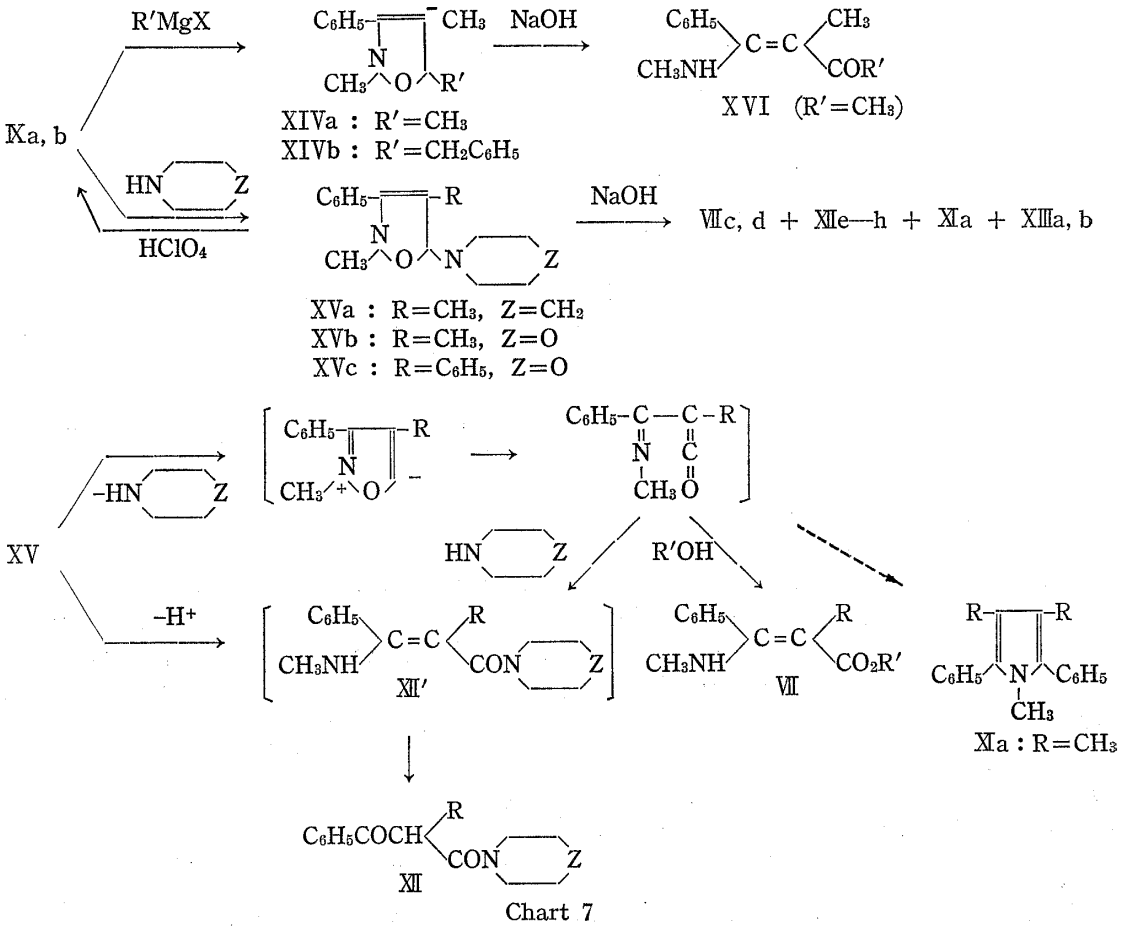


Chart 7

IXa, b on treatment with perchloric acid. The structures of XIV and XV were established by the IR (absence of carbonyl bands), UV and NMR spectra (Fig. 1). Treatment of XIV with sodium hydroxide in aqueous ethanol gave the β-methylaminoketones (XVI). Similar treatment of XV gave the ester VII and the acid amide XII along with a small amount of the pyrrole XIa (only from XVa and b) and the ketone XIII. Solvolysis of XV with methanol gave the ester VII as major product and the acid amide XII as minor product. It is likely that ring opening by deprotonation from XIV and XV yield XVI and XII', respectively. Formation of VII and XIa may be explained as occurring *via* ketene intermediate formed through departure of the respective amine from XV. However, the detailed mechanism of the formation of XI from the possible intermediate is not clear at present.

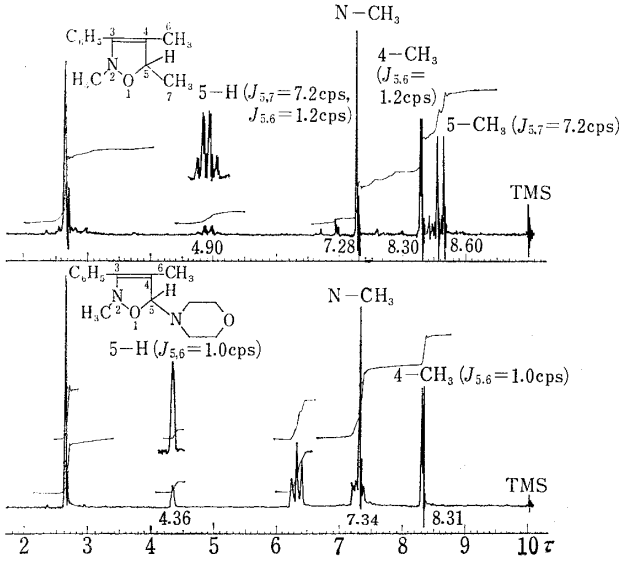


Fig. 1. Nuclear Magnetic Resonance Spectra of XIVa[a] and XVb in $CDCl_3$ (60 Mcps)

a) The NMR spectrum of XIVa was accompanied with the signals of decomposition products due to its instability.

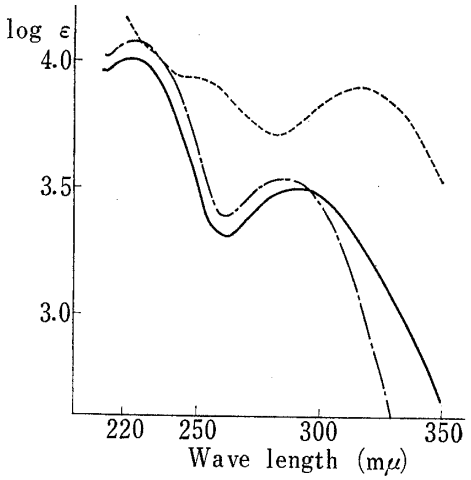


Fig. 2. Ultraviolet Absorption Spectra of XIVa (——), XVb (-·-·-) and XVc (-----)

Experimental

All melting points were taken on a Kofler hot stage and are uncorrected. Solvents were removed *in vacuo*. IR spectra were recorded with a Koken Infrared Spectrophotometer, Model IR-S. UV spectra were taken on a Hitachi Recording Spectrophotometer, EPS-2. NMR spectra were measured with a Varian A-60 analytical NMR spectrometer with tetramethylsilane as an internal reference. Chemical shifts were given in τ values and coupling constants (J) in cps.

4-Methyl-3-phenylisoxazole (VIIIa)——A solution of benzohydroxamyl chloride in ether (200 ml), freshly prepared from benzaldoxim (73 g) and Cl_2 (56 g) by the general procedure,[10] was added dropwise to a solution of N-(1-propenyl)piperidine[11] (70 g) and NEt_3 (110 g) in ether (1 liter) with stirring and cooling in an ice bath and the mixture was refluxed for 2 hr, then washed with H_2O and evaporated. The residue was dissolved in a solution of conc. aq. HCl (90 ml) in AcOH (140 ml) and the mixture was refluxed 6 hr, then evaporated. To the residue was added H_2O and the mixture was extracted with ether. Evaporation of the solvent left a brown liquid, which was distilled *in vacuo* to give pale yellow liquid (70.0 g), bp 100° (0.6 mmHg). NMR (in $CDCl_3$) τ: 1.79 (5-H, quartet, J=1.2 cps), 7.88 (4-CH_3, doublet, J=1.2 cps). *Anal.* Calcd. for $C_{10}H_9ON$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.70; H, 5.85; N, 8.67.

3,4-Diphenylisoxazole (VIIIb)[12]——Treatment of benzohydroxamyl chloride (16.0 g) with styryl acetate[13] (20.0 g) and NEt_3 (20.0 g) in ether (350 ml) by a similar manner as the above gave a brown liquid. It was

10) *a*) A. Werner and H. Buss, *Chem. Ber.*, **27**, 2197 (1894); *b*) A. Werner and C. Block, *Chem. Ber.*, **32**, 1979 (1899).
11) G. Opitz, H. Hellmann and H.W. Schubert, *Ann.*, **623**, 112 (1959).
12) E.P. Kohler and A.R. Davis, *J. Am. Chem. Soc.*, **52**, 4527 (1930).
13) P.Z. Bedoukian, *J. Am. Chem. Soc.*, **66**, 1325 (1944).

dissolved in a solution of NaOH (20 g) in 60% aq. EtOH and the mixture was heated at 50° for 1 hr. After cooling the precipitated 3,4-diphenylfuroxan (4.1 g) was filtered off and the filtrate was neutralized with AcOH, then evaporated. To the residue was added H_2O and the mixture was extracted with $CHCl_3$. Evaporation of the solvent left a brown liquid, which was chromatographed on alumina with benzene to give crude VIIIb (6.42 g, 23.4%). Recrystallization from *n*-hexane gave colorless needles, mp 88—89°. (lit.[12] mp 91°). NMR (in $CDCl_3$) τ: 1.27 (5-H, singlet). *Anal.* Calcd. for $C_{15}H_{11}ON$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.45; H, 5.16; N, 6.55.

3-Phenylisoxazole (VIIIc)——This compound was prepared in 64.2% yield according to the procedure reported by Paul and Tchelitcheff.[14]

Quaternary Salts (V and IX)——2-Ethyl-3,4-diphenylisoxazolium chloroferrate (V) was prepared by using Kohler's original procedure and the other by the following general procedure. A mixture of VIII (0.15 mole) and dimethyl sulfate (0.15 mole) was first heated to 60°, then to 80° over a period of 2 hr, and finally to 110° for 1 hr. After cooling, the mixture was added to a solution of $NaClO_4$ (0.16 mole) in H_2O (500 ml), and the precipitated perchlorate was filtered off, washed with H_2O and recrystallized from EtOH. 2,4-Dimethyl-3-phenylisoxazolium perchlorate (IXa) (72.7% yield), mp 151—153°, NMR (in CD_3CN) τ: 1.10 (5-H, quartet, J=1.2 cps), 5.78 (N-CH_3, singlet), 7.84 (4-CH_3, doublet J=1.2 cps). *Anal.* Calcd. for $C_{11}H_{12}O_5NCl$: C, 48.11; H, 4.40; N, 5.10. Found: C, 48.00; H, 4.37; N, 5.05.

3,4-Diphenyl-2-methylisoxazolium perchlorate (IXb) (69.2% yield), mp 147—148°, NMR (in CD_3CN) τ: 0.81 (5-H, singlet), 5.74 (N-CH_3, singlet). *Anal.* Calcd. for $C_{16}H_{14}O_5NCl$: C, 57.24; H, 4.20; N, 4.17. Found: C, 56.94; H, 4.11; N, 4.11.

2-Methyl-3-phenylisoxazolium perchlorate (IXc) (71.4% yield), mp 190—191°, NMR (in CD_3CN) τ: 0.96 (5-H, doublet, J=2.2 cps), 2.62 (4-H, doublet, J=2.2 cps), 5.64 (N-CH_3, singlet). *Anal.* Calcd. for $C_{10}H_{10}O_5NCl$: C, 46.26; H, 3.88; N, 5.40. Found: C, 45.78; H, 3.86; N, 5.30.

β-Ethylamino- and β-Methylamino-α-phenylcinnamic Anhydride (Xa and Xb)——[Method A] Using Kohler's original procedure, the salt (V or IXb) (0.9 mmole) was shaken with NaOH (0.5 g) in ice–water (5 ml) and benzene (20 ml) until all of the salt was decomposed. Separation of benzene layer and evaporation of the solvent left a solid, which was recrystallized from benzene–petr. ether. Xa (40% yield), mp 141—142° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3210, 1671, 1622. NMR (in $CDCl_3$) τ: 0.22 (NH), 7.02 (NH-CH_2–, quartet of doublet). *Aanl.* Calcd. for $C_{34}H_{32}O_3N_2$: C, 79.04; H, 6.25; N, 5.42. Found: C, 79.12; H, 6.37; N, 5.33. Xb (15% yield), mp 136—137° (decomp.), IR ν_{max}^{Nujol} cm^{-1}: 3225, 1674, 1628. NMR (in $CDCl_3$) τ: 0.25 (NH), 7.35 (N-CH_3, doublet, J=6.0 cps). *Anal.* Calcd. for $C_{32}H_{28}O_3N_2$: C, 78.66; H, 5.78; N, 5.73; mol. wt., 488.56. Found: C, 78.36; H, 5.79; N, 5.58; mol. wt., 499.

[Method B] To a solution of IXb (3.35 g) and H_2O (0.09 ml) in CH_3CN (25 ml) was added NEt_3 (2.1 ml) dropwise with stirring and cooling in an ice bath and the mixture was stirred at 0° for 1.5 hr. The precipitated crystalline product was collected by filtration and recrystallized from benzene-*n*-hexane to give Xb (2.308 g) as colorless needles, mp 136—137° (decomp.).

Methanolysis of Xb——A solution of Xb (0.1 g) in MeOH (10 ml) was refluxed for 10 min, then evaporated. The residue was chromatographed on alumina with benzene to give a crystalline product (0.044 g). Recrystallization from petr. ether gave methyl β-methylamino-α-phenylcinnamate (VIIb) as pale yellow plates, mp 104—105°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3270, 1633. *Anal.* Calcd. for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.44; H, 6.45; N, 5.14.

Reaction of IX with Sodium Alcoholate——To a solution of Na (0.46 g) in alcohol (30 ml) was added IX (10 mmole) portionwise with stirring and cooling in an ice bath and the mixture was stirred at 50° for 10 min, then cooled, neutralized with AcOH and evaporated. To the residue was added H_2O and the suspension was extracted with ether. Evaporation of the solvent left VII, which was purified by recrystallization from petr. ether or by distillation *in vacuo*. Methyl α-methyl-β-methylaminocinnamate (VIIc) (94.0% yield), mp 64—65°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3290, 1638. *Anal.* Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.86; H, 7.15; N, 6.84. Ethyl α-methyl-β-methylaminocinnamate (VIId) (92.6% yield), bp 111° (0.1 mmHg). IR ν_{max}^{film} cm^{-1}: 3230, 1644. *Anal.* Calcd. for $C_{13}H_{17}O_2N$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.23; H, 7.89; N, 6.46. Ethyl β-methylamino-α-phenylcinnamate (VIIe) (96.4% yield), mp 87—88°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3250, 1627. *Anal.* Calcd. for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.76; H, 6.87; N, 5.06.

A solution of VIId (0.5 g) and NaOH (0.2 g) in 50% aq. EtOH was stirred at 50° for 10 min, then cooled, neutralized with 10% aq. HCl and extracted with ether. Evaporation of the solvent left a liquid, which was chromatographed on alumina with benzene to give ethyl 2-benzopropionate as colorless liquid (0.33 g). It was identified with authentic sample[6] by comparison of their infrared spectra.

Reaction of IXa with NaOH in Aqueous Medium——A mixture of IXa (2.73 g) with benzene (30 ml) was shaken with NaOH (0.5 g) in ice–water (20 ml) until all of the salt was decomposed. The benzene layer was separated, then evaporated. The residue was chromatographed on alumina with petr. ether to give 2,5-diphenyl-1,3,4-trimethylpyrrole (XIa) (0.395 g) as 1st fraction, which was recrystallized from EtOH to afford colorless

14) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. France*, **1962**, 2215.

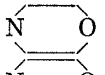
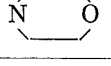
needles, mp 101—102°. *Anal.* Calcd. for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found: C, 88.11; H, 7.25; N, 5.49. As 2nd fraction, propiophenone (XIIIa) (0.075 g) was isolated. The water phase was neutralized with 10% aq. HCl and extracted with CH_2Cl_2. Evaporation of the solvent and recrystallization of the resulting residue from CCl_4 gave colorless needles (XIIa), mp 79—81°, which was identified with 2-benzopropionic acid[7] by comparison of their infrared spectra.

Reaction of IXa with Ammonia in Methanolic Medium——A solution of IXa (2.73 g) in 30% MeOH–NH_3 (20 ml) was stirred at 50° for 2 hr, then evaporated. To the residue was added H_2O and the mixture was extracted with CH_2Cl_2. Evaporation of the solvent left a brown liquid, which was chromatographed on alumina with petr. ether, then with benzene and finally with $CHCl_3$ to give following products: XIa (0.20 g, 15.4%) at 1st fraction (petr. ether); 3,4-dimethyl-2,5-diphenylpyrrole (XIb) (0.21 g, 17.1%) as 2nd fraction (benzene), which was recrystallized from EtOH to give colorless needles, mp 143—144°. *Anal.* Calcd. for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66. Found: C, 87.57; H, 6.68; N, 5.90; and XIIb (0.19 g, 10.7%), listed in Table I, as last fraction ($CHCl_3$).

3,4-Dimethyl-2,5-diphenyl- and 2,5-Diphenyl-1,3,4-trimethylpyrrole (XIb and XIa)——These compounds were prepared according to the similar procedure as that for 2,5-diphenylpyrrole described by Allen, *et al.*[15] A mixture of *trans* 2,3-dibenzoyl-2-butene[16] (0.396 g) and PtO_2 (0.03 g) in EtOH (30 ml) was shaken with hydrogen under atmospheric pressure until 57 ml of hydrogen was absorbed. The catalyst was filtered off and the filtrate was evaporated to give crude 2,3-dibenzoylbutane containing a small amount of 3,4-dimethyl-2,5-diphenylfuran as a viscous oil. To this was added 17% ethanolic ammonia (10 ml) and the solution was heated at 160° for 6 hr in a sealed tube, then evaporated. The residue was chromatographed on alumina with benzene to give colorless crystals (0.025 g). Recrystallization from petr. ether gave colorless needles, mp 142—144°, which were identified with XIb described above by comparison of their IR spectra. The product obtained by catalytic hydrogenation of *trans* 2,3-dibenzoyl-2-butene (0.396 g) was treated with 30% ethanolic methylamine by the similar manner as the above to give a small amount of XIa, along with 3,4-dimethyl-2,5-diphenylfuran (0.163 g).

Reaction of IXa, b with Amines——A solution of IX (5 mmole) and amine (10 mmole) in CH_2Cl_2 (25 ml) was stirred at room temperature for 3 hr, then washed with H_2O and evaporated. The residue was chromatographed on alumina with petr. ether and subsequent $CHCl_3$ to give XIa, trace of XIII, and XII. XII was purified by recrystallization from benzene–petr. ether and listed in Table I.

Table I. $C_6H_5COCH\langle^{R}_{COR'}$ XII

Compound No.	R	R′	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	Yield (%)	Yield of XIa (%)
XIIa[A]	CH_3	OH	79— 81	$C_{10}H_{10}O_3$							27.0	33.2
b	CH_3	NH_2	150—151	$C_{10}H_{11}O_2N$	67.78	6.26	7.91	67.42	6.33	8.23	24.9	B
c	CH_3	$NHCH_3$	137—138	$C_{11}H_{13}O_2N$	69.09	6.85	7.33	69.00	6.73	7.35	65.5	6.1
d	CH_3	NHC_3H_{7-n}	106—107	$C_{13}H_{17}O_2N$	71.20	7.82	6.39	71.49	7.83	6.57	45.3	22.8
e	CH_3	$NHCH_2CH_2C_6H_5$	99—100	$C_{18}H_{19}O_2N$	76.84	6.81	4.98	77.00	6.79	5.07	48.7	15.4
f	CH_3		96— 97	$C_{15}H_{19}O_2N$	73.44	7.81	5.71	73.51	7.86	5.76	68.8	trace
g	CH_3		102—103	$C_{14}H_{17}O_3N$	67.99	6.93	5.66	67.94	6.95	5.57	70.3	trace
h	C_6H_5		182—184	$C_{19}H_{19}O_3N$	73.76	6.19	4.53	73.86	6.08	4.48	64.2	—

A: Lit.[7] mp 82—83° B: XIa: 15.4%; XIb: 17.1%

3-Phenyl-2,4,5-trimethyl-Δ^3-isoxazoline (XIVa)——To a solution of CH_3MgJ in ether (30 ml), prepared from Mg (0.486 g) with CH_3J (3.1 g) in ether by the general procedure,[17] was added IXa (2.73 g) portionwise with stirring and cooling in an ice-bath and the mixture was stirred at 0° for 2 hr. To the mixture was added a solution of NH_4Cl (5 g) in H_2O (10 ml) dropwise with vigorous stirring and then ethereal phase was separated. Evaporation of the solvent left a yellow liquid, which was distilled *in vacuo* to give colorless liquid (1.20 g, 63.5%), bp 70—72° (0.02 mmHg). *Anal.* Calcd. for $C_{12}H_{15}ON$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.47; H, 8.02; N, 7.18.

15) C.H. Allen, D.M. Young and M.G. Gilbert, *J. Org. Chem.*, **2**, 235 (1937).
16) R.E. Lutz and R.J. Taylor, *J. Am. Chem. Soc.*, **55**, 1593 (1933).

5-Benzyl-2,4-dimethyl-3-phenyl-Δ^3-isoxazoline (XIVb)——Treatment of IXa (2.73 g) with $C_6H_5CH_2$-MgCl by the similar manner as the above gave a pale yellow liquid (2.23 g, 84.0%), bp 159° (0.05 mmHg). NMR (in $CDCl_3$) τ: 4.83 (5-H, triplet, $J=4.5$ cps of quartet, $J=1.1$ cps), 7.06 ($C_6H_5CH_2$–, doublet, $J=4.5$ cps), 7.52 (NCH_3, singlet), 8.34 (4-CH_3, doublet, $J=1.1$ cps). *Anal.* Calcd. for $C_{18}H_{19}ON$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.30; H, 7.24; N, 4.82. Its perchlorate: colorless needles (from EtOH), mp 166—167°. *Anal.* Calcd. for $C_{18}H_{20}O_5NCl$: C, 59.10; H, 5.51; N, 3.83. Found: C, 59.18; H, 5.40; N, 3.69.

2,4-Dimethyl-3-phenyl-5-piperidino-Δ^3-isoxazoline (XVa)——To a solution of piperidine (0.85 g) in CH_2Cl_2 (10 ml) was added IXa (1.37 g) portionwise with stirring and cooling in an ice–bath and the mixture was stirred at 0° for 30 min, then evaporated. To the residue was added ether and insoluble salt was filtered off. Evaporation of ether left a crystalline product (1.28 g), which was recrystallized from petr. ether to give colorless needles, mp 87—89°. NMR (in $CDCl_3$) τ: 4.29 (5-H, quartet, $J=$ 1.0 cps), 7.33 (NCH_3, singlet), 8.34 (4-CH_3, doublet, $J=1.0$ cps). *Anal.* Calcd. for $C_{16}H_{22}ON_2$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.38; H, 8.56; N, 10.87.

2,4-Dimethyl-3-phenyl-5-morpholino-Δ^3-isoxazoline (XVb)——Treatment of IXa (2.73 g) with morpholine (1.8 g) in CH_2Cl_2 (20 ml) by the similar manner as the above gave colorless prisms (2.55 g), mp 66—67°. *Anal.* Calcd. for $C_{15}H_{20}O_2N_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.19; H, 7.84; N, 10.69. Passage of XVb (0.20 g) through an alumina column with CH_2Cl_2 gave XIIg (0.157 g) listed in Table I.

3,4-Diphenyl-2-methyl-5-morpholino-Δ^3-isoxazoline (XVc)——Treatment of IXb (1.01 g) with morpholine (0.52 g) in CH_2Cl_2 (10 ml) by the similar manner as the above gave colorless plates (0.962 g), mp 112—113°. NMR (in $CDCl_3$) τ: 4.07 (5-H, singlet), 7.27 (NCH_3, singlet). *Anal.* Calcd. for $C_{20}H_{22}O_2N_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.61; H, 6.83; N, 8.19.

Methyl α-Methyl-β-methylaminostyryl Ketone (XVI)——A solution of XIVa (1.8 g) and NaOH (1.0 g) in 50% aq. EtOH (10 ml) was stirred at 50° for 1 hr, then cooled, neutralized with 10% aq. HCl and extracted with CH_2Cl_2. Evaporation of the solvent left a brown liquid, which was chromatographed on alumina with benzene to give recovered XIVa (0.78 g) and subsequent colorless crystalline product (0.13 g). Recrystallization from 70% aq. EtOH gave colorless needles, mp 66—67°. IR ν_{max}^{Nujol} cm^{-1}: 1561. NMR (in $CDCl_3$) τ: 7.41 (NCH_3, doublet $J=5.3$ cps), 7.83 ($COCH_3$, singlet), 8.46 (CH_3, singlet). *Anal.* Calcd. for $C_{12}H_{15}ON$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.36; H, 7.66; N, 7.51.

Reaction of XVb with NaOH in Aqueous Ethanol——A mixture of XVb (0.81 g) and NaOH (0.5 g) in 80% aq. EtOH was heated on a water bath for 10 min, then cooled and extracted with ether. Evaporation of the solvent left a brown liquid, which was chromatographed on alumina with petr. ether and subsequent $CHCl_3$ to give following products: a trace of XIa (1st fraction); VIId (0.29 g) containing a trace of propiophenone (2nd fraction); and XIIg (0.22 g) (last fraction).

Methanolysis of XVb and XVc——A solution of XVb (0.4 g) in MeOH (20 ml) was refluxed for 20 min, then evaporated. The residue was chromatographed on alumina with benzene and subsequent $CHCl_3$ to give following products: VIIc (0.224 g, 71.5%) (1st fraction); and XIIg (0.095 g, 25.2%) (2nd fraction).

Similar treatment of XVb (0.2 g) in MeOH (20 ml) gave VIIb (0.098 g, 59.4%) and XIIh (0.052 g, 28.3%).

Acknowledgement The authors thank Professor Emeritus E. Ochiai of Tokyo University and Dr. K. Takeda, Director of this Laboratory, for their helpful guidance and encouragement. They are indebted to members of the Physical Chemistry Department for the spectral measurements, to members of the Analysis Room for the elemental analysis and to Miss Y. Hayashi for the technical assistance.

17) H. Gilman and W.E. Catlin, *Org. Syn.*, Col. Vol. I, 471 (1948).