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Isoxazoles. XIX.[1] Synthesis and Cleavage Reaction of Some 3,4-Disubstituted Isoxazoles

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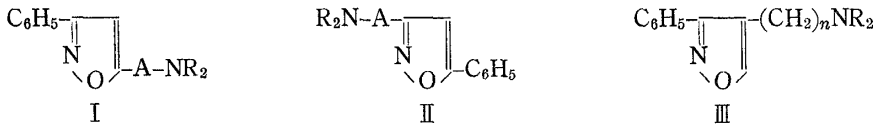
Nine bicyclic isoxazolines (IVa—g and Va—b) were prepared by 1,3-dipolar cycloaddition of nitrile oxides to the following heterocyclic olefins: 2,3- and 2,5-dihydrofurans, 5-methyl-2,3-dihydrofuran, 2,3-dihydropyran, and N-acetyl-2-piperidein. Acid-catalized cleavage of IVa—d gave the corresponding 4-substituted 3-phenylisoxazoles (VIa—c and IIIg). Nine 4-aminoalkyl-3-phenylisoxazoles (IIIa—i) were prepared for pharmacological testings in comparison with those of 3- and 5-aminoalkyl analogs (I and II). Base-catalized cleavage of the adducts (IVa—c and Va) was also investigated and in some cases the lactones (XIIa and XIIb) were obtained besides the isoxazloes (VIa and VIb). In this connection the Hofmann reactions of the bicyclic isoxazoline-3-carbonamides (IVe′ and IVf′) were studied.

In the preceding paper[1] of this series, a number of 5-aminoalkyl-3-phenyl-, and 3-aminoalkyl-5-phenyl-isoxazoles (I and II) together with some related derivatives have been prepared. Some of the compounds have been proved to exhibit a variety of pharmacological activities: hypothermic, analgesic, antiinflammatory and antitussive.



I II III

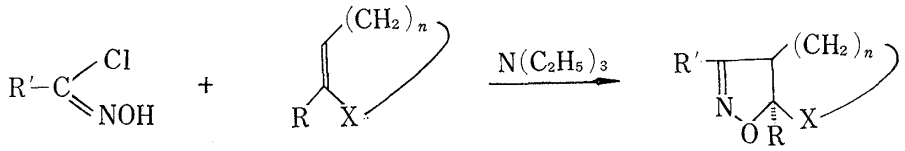
A=alkylene, hydroxyaylkylene

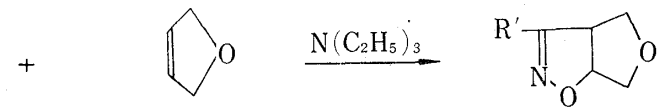
Chart 1

It appeared of interest to synthesize an additional series of compounds, 4-aminoalkyl-3-phenylisoxazoles (III) for comparison of the pharmacological properties between this and the previous two series (I and II). This paper describes the synthesis of III and some relevant compounds, including their cleavage reactions.

Although syntheses of a number of 3,4-disubstituted isoxazoles have been reported,[3] few methods seemed to be suitable for the presnet purpose. However, an elegant synthesis of 3-aryl-4-*n*-hexylisoxazole involving the cycloaddition reaction of arylnitrile oxide and 1-morpholino-2-octene followed by deamination has been reported by Bianchetti, *et al.*, recently.[4] Paul and Tchelitcheff[5] described the synthesis of some bicyclic isoxazoline derivatives by cycloaddition of nitrile oxides and heterocyclic olefins, wherein they obtained the bicyclo adducts (IVa and IVb) from 2,3-dihydrofuran and 2,3-dihydropyran, respectively, when benzonitrile oxide was used as a dipole. If the ether bond scission and simultaneous aromatization of IVa and IVb proceed in a similar way as the above deamination, the requisite intermediates for III, 4-hydroxyalkyl-3-phenylisoxazoles (VIa and VIb) may be produced.

1) Part XVIII: H. Kanō, I. Adachi, R. Kido, and K. Hirose, *J. Med. Chem.*, **10**, 411 (1967).
2) Location: *Fukushima-ku, Osaka.*
3) For example, see *a*) E.P. Kohler and A.R. Davis, *J. Am. Chem. Soc.*, **52**, 4520 (1930); *b*) R. Justoni, *Rend. Ist. Lomardo. Sci.*, **71**, 407 (1938); *c*) N.K. Kochetkov, E.D. Khomutova, and M.V. Bazilevskii, *Zhur. Obshchei. Khim.*, **28**, 2736 (1958); *d*) F. Korte and K. Störiko, *Chem. Ber.*, **94**, 1956 (1961).
4) G. Bianchetti, D. Pocar, and P.D. Croce, *Gazz. Chim. Ital.*, **193**, 1714 (1963).
5) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. France*, 2215 (1962).

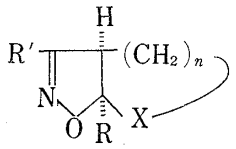




$R'=C_6H_5$, $CO_2C_2H_5$; R=H, CH_3; $n=2,3$; X=O, $NCOCH_3$

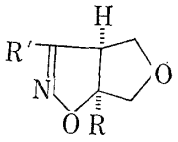
Chart 2

TABLE I. Bicyclo-1,3-adducts



IV

and



V

Compound No.	R′	R	n	X	Yield[a] (%)	bp [°C(mm)] or mp (°C)	Formula
IVa	C_6H_5	H	2	O	95.2	105—106	$C_{11}H_{11}O_2N$
IVb	C_6H_5	H	3	O	40.4	84—85	$C_{12}H_{13}O_2N$
IVc	C_6H_5	CH_3	2	O	63.2	68—69	$C_{12}H_{13}O_2N$
IVd	C_6H_5	H	3	N-$COCH_3$	51.1	143—144	$C_{14}H_{16}O_2N_2$
IVe′	$CONH_2$	H	2	O	62.2	169—170	$C_6H_8O_3N_2$
IVf′	$CONH_2$	H	3	O	28.5	183—184	$C_7H_{10}O_3N_2$
IVg′	$CONH_2$	H	3	N-$COCH_3$	7.1	156—157	$C_9H_{13}O_3N_3$
Va	C_6H_5	H			77.5	64—65	$C_{11}H_{11}O_2N$
Vb′	$CONH_2$	H			15.8	171—173	$C_6H_8O_3N_2$

Compound No.	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	τ value of R (in $CDCl_3$) (multiplicity,[b] J, in cps)
IVa	69.82	5.86	7.40	70.31	5.78	7.59	3.75(d, 6.3)
IVb	70.92	6.45	6.89	71.25	6.57	7.27	3.95(d, 8.0)
IVc	70.92	6.45	6.89	71.14	6.62	6.76	8.28(s,)
IVd	68.83	6.60	11.47	68.88	6.48	11.63	3.81(d, 8.2)
IVe′	46.15	5.16	17.94	46.42	5.43	17.81	3.71(d, 5.7)
IVf′	49.40	5.92	16.46	49.26	6.20	16.54	4.03(d, 8.0)
IVg′	51.18	6.20	19.90	51.24	6.39	19.88	3.46(d, 8.2)
Va	69.82	5.86	7.40	70.11	5.82	7.60	4.70(q, 9.3; 3.6)
Vb′	46.15	5.16	17.94	46.33	5.02	18.07	

a) Based on the starting hydroxamyl chloride *b*) d=doublet s=singlet q=quartet

However, the reported yields of IVa and IVb are 40% and 2%, respectively, probably because the oxide is liable to dimerize into furoxan derivative.[6,7] The present reaction, to suppress the dimerization, was run by the similar improved procedure described previously[1] (addition of a hydroxamyl chloride to a benzene solution of a dipolarophile and triethylamine). The following adducts were obatined in considerable yields by the improved procedure. Two known hydroxamyl chlorides: benzohydroxamyl chloride and ethyl chloroximinoacetate underwent reaction with the five heterocyclic olefins: 2,3- and 2,5-dihydrofurans, 5-methyl-2,3-dihydrofuran, 2,3-dihydropyran and N-acetyl-2-piperidein to give the corresponding adducts. Five adducts (IVa—d and Va) and four amides (IVe'—g' and Vb') derived from the adducts (IVe—g and Vb)[8] are listed in Table I.

The adducts (IVa—c) were treated with hydrochloric acid in ethanol to give the 4-hydroxyalkyl derivatives (VIa—c) in good yields. Similar treatment of IVd resulted in the C–N bond cleavage and hydrolysis of the N-acetyl group to yield 4-(3-aminopropyl)-3-phenylisoxazole (IIIg). However, the compound (Va) did not undergo cleavage under

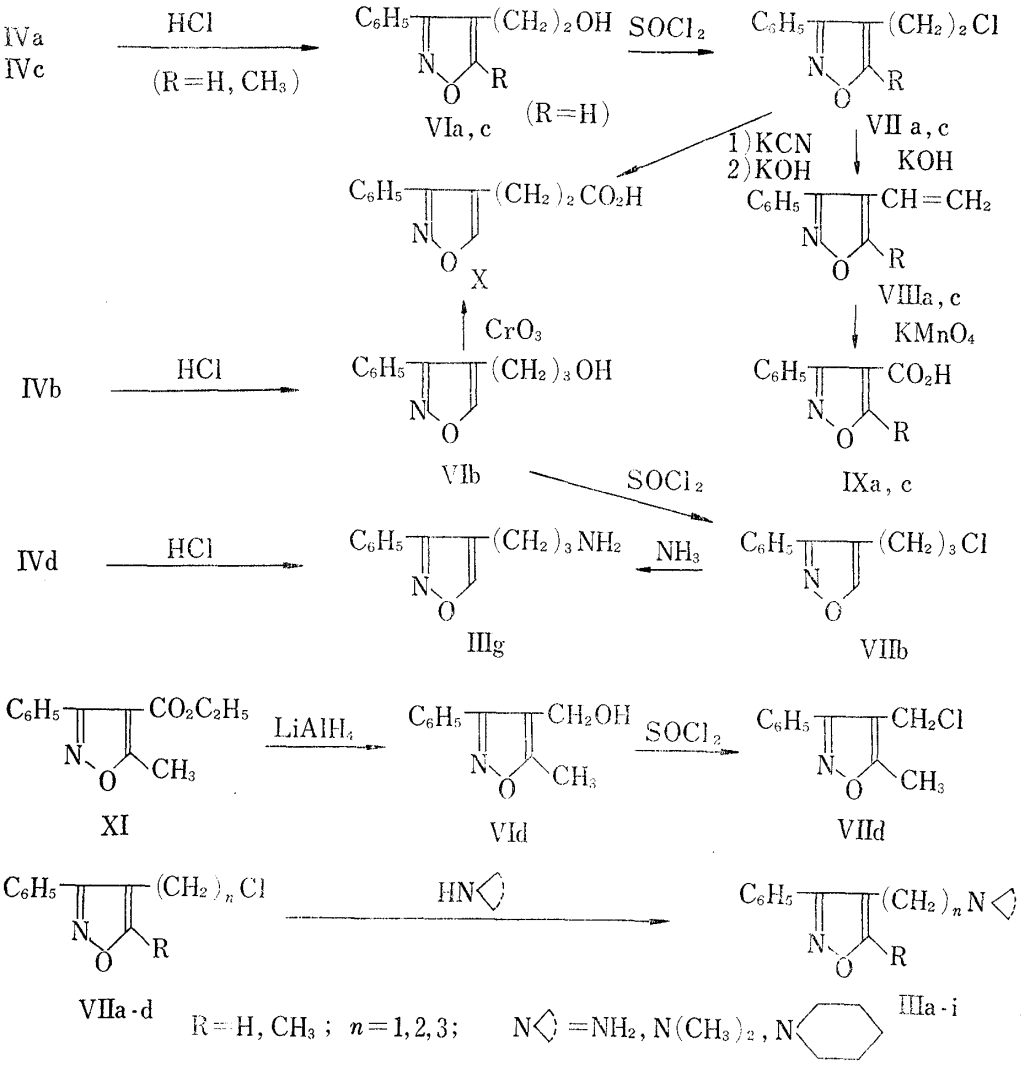
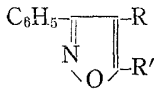


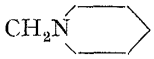
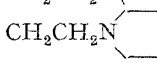
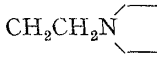
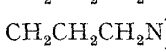
Chart 3

6) A. Quilico, "The Chemistry of Heterocyclic Compounds," **17**, R.H. Wiley, ed., Interscience Publishers, Inc., New York, 1962, p. 19.
7) R. Huisgen, *Angew. Chem.*, **75**, 604 (1963).
8) The adducts (IVe—g and Vb) were all liquids and difficult to isolate in pure state, so they were converted to crystaline amides.

similar conditions. The 4–hydroxyalkyl derivatives (VIa—c) were converted to the corresponding 4–chloroalkyl derivatives (VIIa—c). The structures assigend to the products (VIa—c) were confirmed by the following reactions. Two respective vinyl derivatives (VIIIa and VIIIc) were obtained by treatment of VIIa and VIIc with methanolic potassium hydroxide. These were oxidized to the corresponding carboxylic acids (IXa and IXc) with potassium permanganate in acetone. The physical property of VIIIc agreed well with that of 5–methyl–3–phenyl–4–vinylisoxazole recorded in the literature[9] and the acid (IXc) was identical with authentic sample of 5–methyl–3–phenyl–4–isoxazolecarboxylic acid.[10] The structure of VIIIa and IXa were confirmed by comparison of their ultraviolet (UV) and infrared (IR) spectra with those of VIIIc and IXc (see Experimental). Structural correlation between VIIa and VIb was accomplished by the formation of the same acid (X) from both VIIa and VIb as shown in Chart 3. The 3–chloropropyl derivative (VIIb) was treated with ethanolic ammonia gave the same amine (IIIg) as obtained from IVd. An additional 4–

Table II. 4–Aminoalkyl–3–phenyl–, 4–Aminoalkyl–5–methyl–3–phenylisoxazoles and Their Hydrochlorides



Compound No.	R	R′	Yield (%)	bp [°C(mm)][a] or mp (°C)	mp[b] (°C)	Formula
IIIa	$CH_2N(CH_3)_2$	CH_3	87.5	54—56	203—205	$C_{13}H_{16}ON_2 \cdot HCl$
IIIb	CH_2N 	CH_3	92.6	40—41	183—185	$C_{16}H_{20}ON_2 \cdot HCl$
IIIc	$CH_2CH_2NH_2$	H	44.0	135(0.6)	200—202	$C_{11}H_{12}ON_2 \cdot HCl$
IIId	$CH_2CH_2N(CH_3)_2$	H	93.8	128(0.3)	155—156.5	$C_{13}H_{16}ON_2 \cdot HCl$
IIIe	CH_2CH_2N 	H	87.0	161(0.5)	186—187	$C_{16}H_{20}ON_2 \cdot HCl$
IIIf	CH_2CH_2N 	CH_3	48.4	—	215—216	$C_{17}H_{22}ON_2 \cdot HCl$
IIIg	$CH_2CH_2CH_2NH_2$	H	58.4	142(0.2)	150—151	$C_{12}H_{14}ON_2 \cdot HCl$
IIIh	$CH_2CH_2CH_2N(CH_3)_2$	H	75.4	136(0.4)	166—167.5	$C_{14}H_{18}ON_2 \cdot HCl$
IIIi	$CH_2CH_2CH_2N$ 	H	62.9	166(0.4)	160—161	$C_{17}H_{22}ON_2 \cdot HCl$

Compound No.	Analysis (%) Calcd. C	H	N	Found C	H	N
IIIa	61.78	6.78	11.08	61.56	6.90	11.15
IIIb	65.63	7.23	9.57	65.86	7.34	9.56
IIIc	58.80	5.83	12.47	58.59	5.87	12.86
IIId	61.78	6.78	11.08	61.66	7.05	10.95
IIIe	65.63	7.23	9.57	65.76	7.49	9.47
IIIf	66.55	7.56	9.13	66.32	7.74	9.40
IIIg	60.38	6.33	11.74	59.84	6.37	11.40
IIIh	63.03	7.18	10.50	63.43	7.32	10.54
IIIi	66.55	7.56	9.13	66.64	7.50	9.19

a) base *b*) hydrochloride

9) P.V. Finzi, P.L. Caramella, and P. Grünanger, *Annali. Di Chimica*, **55**, 1233 (1965) (*Chem., Abstr.*, **65**, 3853 (1966)).
10) A. Quilico and R. Fusco, *Gazz. Chim. Ital.*, **67**, 589 (1937).

chloroalkyl derivative (VIId) was prepared stepwise from the corresponding 4-ethoxycarbonyl derivative (XI). Treatment of 4-chloroalkyl derivatives (VIIa—d) with appropriate amines gave the objective 4-aminoalkyl derivatives (IIIa—i) listed in Table II. Several of the compounds proved to exhibit similar pharmacological properties as those of I and II, and the details will be reported elsewhere.

In connection with the acid-catalized cleavage of the adducts (IVa—c), base-catalized cleavage of these compounds has also been investigated. Refluxing a solution of IVa in ethanol with sodium ethylate for one to three hours gave the isoxazole (VIa), a lactone (XIIa) and benzonitrile (XIII). The NMR spectrum of XIIa showed the presnece of a $-(CH_2)_2-$ group (at τ5.77, triplet, J=7.9 cps and at τ7.18, triplet, J=7.9 cps in $CDCl_3$) and the absence of -CH= group. Its IR spectrum in $CHCl_3$ solution exhibited peaks at 3512, 3360, 1696 and 1629 cm^{-1} attributable to a β-aminoacrylate group. Based on these evidence together with its analytical data, the structure of 3-(α-aminobenzylidene)-2-tetrahydrofuranone was assigned to the lactone (XIIa). This structure assignment was confirmed on the bases of the conversion of XIIa to 3-benzoyl-2-tetrahydrofuranone by hydrolysis and to 3-benzoyl-1-propanol by treatment with aqueous sulfuric acid. Similarly, the base-catalized cleavage of IVb gave the corresponding isoxazole (VIb), 3-(α-aminobenzilidene)-2-tetrahydropyrone (XIIb) and benzonitrile (XIII). The IR and NMR spectra of XIIb were consistent with the assigned structure. The lactone (XIIa or XIIb) together with benzonitrile (XIII) could be produced by the same treatment of the corresponding isoxazole (VIa or VIb) with base. In contrast to the cleavage reaction of IVa and IVb, the adduct (IVc) gave the corresponding isoxazole (VIc) exclusively in quantitative yield even on a prolonged refluxing with ethanolic sodium ethylate. A similar cleavage reaction did not undergo with the adduct (Va).

These results suggest that the formation of XII and XIII from IV would involve the route, IV→VI→XII→XIII; the isoxazole derivative (VI) initially formed undergo abstraction of the proton at 5-position followed by N-O bond rupture gives a ketene intermediate (XIV), whose intramolecular cyclization gives the lactone (XII) and a further cleavage of XII

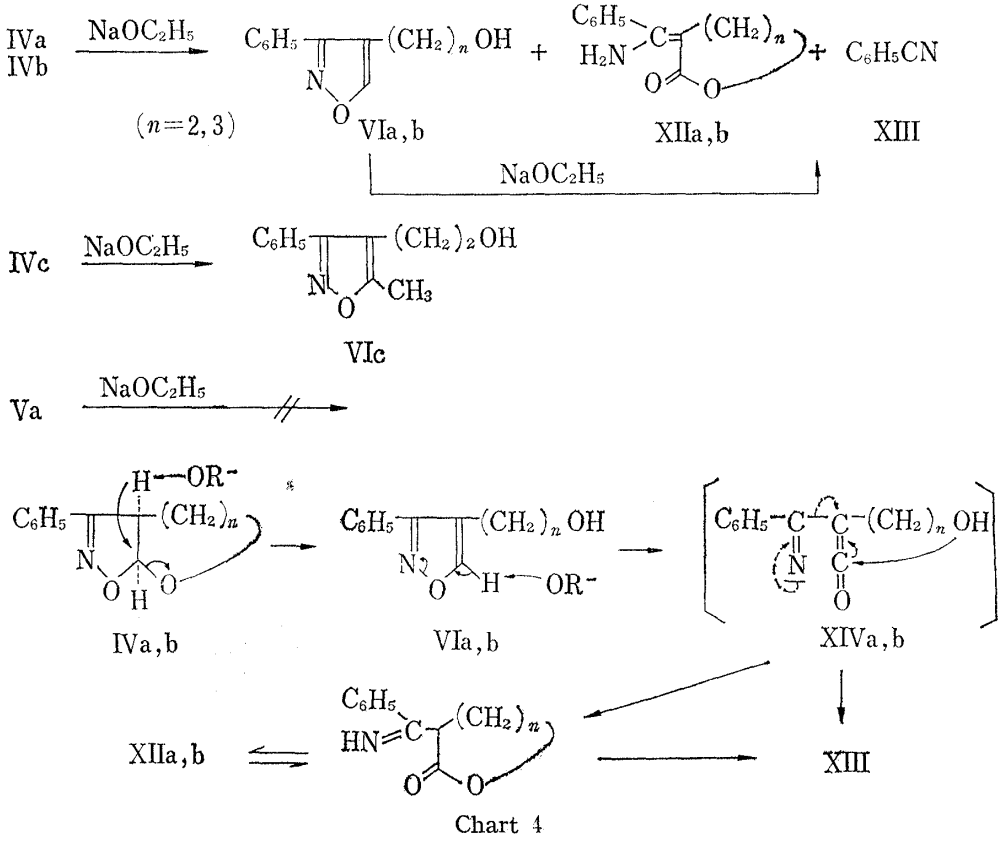


Chart 4

produces benzonitrile (XIII). The cleavage of XII into XIII did indeed proceed, but the direct formation of XIII from XIV may be also involved. Some available reports on the cleavage reactions of 3,4-disubstituted isoxazoles with base have been reported[11] and are consistent with our present results. The yields of the products in the base-catalized cleavage reaction of IVa and IVb in varying conditions are listed in Table III.

The data indicated that the rate of cleavage of IVa is faster than that of IVb and a prolonged reaction causes decrease in yield of VI and increase in that of XII and XIII. A marked difference in cleavage rate between the bicyclic dihydrofuran and dihydropyran was observed in the Hofmann reactions of IVe' and IVf'; IVe' gave the corresponding bicyclic amine (XV) in 82.1% yield and IVf' gave 3-amino-4-hydroxypropylisoxazole (XVI) in 94.4% yield. The structures of the both products were confirmed by their analytical and spectral data (see Experimental). These difference may be explained as arising from the comparative coplanarity of the ether group and the adjacent hydrogen in these bicyclic systems.

Table III. The Yields in the Cleavage Reactions of IVa and IVb in Varying Conditions

Compound	Temp. (°C)	Time (hr)	Yield (%) VI	XII	XIII	IV (recovered)
IVa	50	6	88.3	1.2	trace	0.5
	80 (reflux)	0.1	94.3	0.9	trace	1.1
	80 (reflux)	3	33.5	29.5	22.9	0
IVb	50	0.5	96.3	0	0	0
	80 (reflux)	1	50.3	11.9	16.9	—
	80 (reflux)	3	41.3	17.5	22.2	—

Note: The reaction was carried out with equimolar sodium ethylate in ethanolic solution.

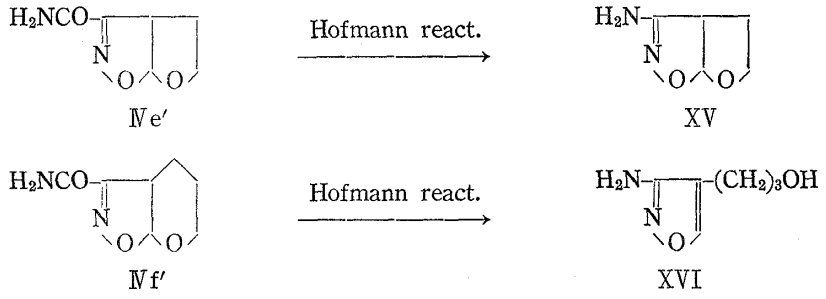


Chart 5

Experimental[12]

Benzohydroxamyl chloride and ethyl chloroximinoacetate were prepared by the reaction of benzaldoxim with Cl_2 in ether[13] and by the reaction of ethyl aminoacetate with HNO_2,[14] respectively. 2,3-Dihydro-

11) N.K. Kochetkov and S.D. Sokolov, "Advance in Heterocyclic Chemistry", **2**, A.R. Katritzky, Ed. Academic Press, New York and London, 1963, p. 402.

12) 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.

13) *a*) A. Werner and H. Buss, *Chem. Ber.*, **27**, 2197 (1894); *b*) A. Werner and C. Block, *Chem. Ber.*, **32**, 1979 (1899).

14) G.S. Skinner, *J. Am. Chem. Soc.*, **46**, 731 (1924).

furan, 5-methyl-2,3-dihydrofuran and N-acetyl-2-piperidein were obtained according to the procedures reported by Paul, *et al.*;[15] Schniepp, *et al.*;[16] Schöpf, *et al.*;[17] respectively.

Bicyclic 1,3-Adducts (IV and V)——The compounds given in Table I were prepared by the following general procedure. To a solution of dipolarophile (0.12 mole) (0.50 mole in the case of 2,3-dihydropyran) and NEt_3(0.12 mole) in benzene (100 ml) was added a solution of hydroxamyl chloride (0.10 mole) in benzene (50 ml) dropwise with stirring and cooling in an ice-water bath and the resulting mixture was stirrred at room temperature for 3 hr, then washed with H_2O, dried over anhyd. $MgSO_4$ and evaporated. In the case of the phenyl derivative, the residue was chromatographed on neutral alumina (activity IV) with benzene to give colorless crystals. Recrystallization from benzene-petr. ether gave the desired product. In the case of the ethoxycarbonyl derivative, to the residue was added 15% EtOH-NH_3 (110 ml) and the solution was stirred at room temperature for 1 hr, then filtered. Evaporation of the solvent left the corresponding amide as colorless crystals which was recrystallized from EtOH-benzene to give the product listed in Table I.

4-Hydroxyalkyl-3-phenyl- and 4-Hydroxyalkyl-5-methyl-3-phenylisoxazoles (VIa—c)——were prepared by the following procedure.

Method A——A solution of IV (0.03 mole) and conc. aq. HCl (5.5 g) in 80% aq. EtOH (45 ml) was refluxed for 3 hr, then evaporated. To the residue was added H_2O and the solution was extractesd with CH_2Cl_2. Evaporation of the solvent gave colorless liquid which was distilled *in vacuo* to give following product (VI).

VIa (99.3% yield), bp 155° (0.5 mm). *Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.54; H, 6.03; N, 7.59.

VIb (92.5% yield), bp 154° (0.2 mm). *Anal.* Calcd. for $C_{12}H_{13}O_2N$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.02; H, 6.56; N, 7.18. Benzoate of VIb, colorless needles (from petr. ether), mp 62°. *Anal.* Calcd. for $C_{19}H_{17}O_3N$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.33; H, 5.69; N, 4.25.

VIc (94.1% yield), bp 153° (0.3 mm). *Anal.* Calcd. for $C_{12}H_{13}O_2N$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.54; H, 6.56; N, 6.75.

Method B (VIc)——To a solution of Na (0.2 g) in EtOH (5 ml) was added IVc (1.02 g) and the solution was refluxed for 3 to 6 hr, then evaporated. To the residue was added H_2O and the solution was extracted with CH_2Cl_2. Evaporation of the solvent left a yellow liquid, which was distilled *in vacuo* to give the above obtained VIc (0.97 g, 95.3%).

4-(3-Aminopropyl)-3-phenylisoxazole Hydrochloride (IIIg)——A solution of IVd (3.66 g) and conc. aq. HCl (4.5 g) in 60% aq. EtOH (45 ml) was refluxed for 15 hr, then evaporated. To the residue was added H_2O and the resulting solution was washed with $CHCl_3$. Evaporation of H_2O left colorless crystals, which was recrystallized from EtOH-benzene to give colorless needles (1.45 g, 40.5%), mp 150—151°. This compound was identified by the comparison of IR spectrum with that prepared from VIIb and NH_3, and listed in Table II.

4-Hydroxymethyl-5-methyl-3-phenylisoxazole (VId)——To a mixture of $LiAlH_4$ (1.52 g) in dry ether (100 ml) was added a solution of ethyl 5-methyl-3-phenyl-4-isoxazolecarboxylate[18] (11.62 g) in dry ether (50 ml) dropwise with stirring and cooling in an ice-water bath and the resulting mixture was refluxed for 2 hr. After cautious addition of H_2O under chilling, the ethereal phase was separated and the aq. layer extracted with ether. The combined ethereal solution was evaporated to give brown crystals, which was recrystallized from petr. benzine to give colorless plates (5.60 g, 59.3%), mp 83—84°. *Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40. Found: C, 70.10; H, 6.01; N 7.36.

4-Chloroalkyl-3-phenyl- and 4-Chloroalkyl-5-methyl-3-phenylisoxazoles (VIIa—d)——were prepared by the following procedure. A solution of VI (0.05 mole) and $SOCl_2$ (17.9 g) in dry ether (20 ml) was refluxed for 2 hr, then evaporated. The residue was distilled *in vacuo* to give colorless liquid. In the case of VIId, the residue was extracted with bioling petr. benzine. After evaporation of the solvent, the crystalline residue was recrystallized from petr. benzine. VIIa (79.2% yield), bp 128° (0.6 mm). *Anal.* Calcd. for $C_{11}H_{10}ONCl$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.82; H, 4.93; N, 6.86. VIIb (97.9% yield), bp 129° (0.3 mm). *Anal.* Calcd. for $C_{12}H_{12}ONCl$: C, 65.02; H, 5.46; N, 6.32. Found: C, 65.15; H, 5.29; N, 6.09. VIIc (74.2% yield), bp 138° (1.0 mm). *Anal.* Calcd. for $C_{12}H_{12}ONCl$: C, 65.02; H, 5.46; N, 6.32. Found: C, 65.31; H, 5.73; N, 6.03. VIId (99.2% yield), mp 50—52°. *Anal.* Calcd. for $C_{11}H_{10}ONCl$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.85; H, 5.07; N, 6.65.

3-Phenyl-4-isoxazolecarboxylic Acid (IXa)——A solution of VIIa (2.12 g) and KOH (1.12 g) in MeOH (10 ml) was refluxed for 1 hr, then evaporated. To the residue was added H_2O and extracted with ether. Evaporation of the solvent left a brown liquid, which was distilled *in vacuo* to give 3-phenyl-4-vinylisoxazole (VIIIa) (1.38 g, 80.7%) as colorless liquid, bp 94° (0.6 mm). IR ν_{max}^{liq} cm^{-1}: 1634, 991, 919 (-CH=CH_2).

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To a solution of VIIIa (0.51 g) in acetone (10 ml) was added $KMnO_4$ (1.23 g) portionwise with stirring and cooling in an ice–water bath and the resulting solution was stirred at room temperature for 2 hr, then evaporated. To the residue was added H_2O and the solution was washed with ether. The aq. solution was acidified with 10% aq. HCl and then extracted with $CHCl_3$. Evaporation of the solvent gave a colorless crystals (0.25 g, 43.4%), which was recrystallized from aq. EtOH to give colorless plates, mp 167—168°. UV λ_{max}^{EtOH} mμ (log ε): 230 (3.974). *Anal.* Calcd. for $C_{10}H_7O_3N$: C, 63.49; H, 3.73; N, 7.40. Found: C, 63.84; H, 3.71; N, 7.48.

5-Methyl-3-phenyl-4-isoxazolecarboxylic Acid (IXc)——A solution of VIIc (1.77 g) and KOH (0.9 g) in MeOH (10 ml) was treated in a similar manner as the above to give 5–methyl–3–phenyl–4–vinylisoxazole (VIIIc) (1.13 g, 76.4%) a colorless liquid, bp 124° (0.2 mm) [Lit., bp 122—123° (1.2 mm)].[9] IR ν_{max}^{liq} cm^{-1}: 1636, 988, 919 (–CH=CH_2). A solution of VIIIc (0.56 g) in acetone (10 ml) was treated with $KMnO_4$ (1.23g) in a similar manner as the above to give colroless needles (0.16 g, 26.0%), mp 191—193°. UV λ_{max}^{EtOH} mμ (log ε): 216 (4.152). This compound was identified by mixed melting point test and IR spectrum comparison with an authentic sample prepared according to the Quilico's method.[10]

β-(3-Phenyl-4-isoxazolyl)propionic Acid (X). Method A——A solution of VIIa(1.04 g) and KCN (1.30 g) in 80% aq. EtOH (20 ml) was refluxed for 2 hr. To this was added a solution of KOH (0.5 g) in 80% aq. EtOH (12 ml) and the resulting solution was refluxed for 6 hr, then evaporated. To the residue was added H_2O and the solution was washed with ether. The aq. solution was acidified with 10% aq. HCl and extracted with $CHCl_3$. Evaporation of the solvent left yellow crystals (0.51 g, 47.5%), which was recrystallized from aq. EtOH to give colorless plates, mp 111—112°. *Anal.* Calcd. for $C_{12}H_{11}O_3N$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.72; H, 5.22; N, 6.29.

Method B——To a solution of VIb (4.32 g) in AcOH (40 ml) was added a solution of CrO_3 (2.80 g) in 80% aq. AcOH (40 ml) dropwise with stirring and cooling in an ice–water bath and the resulting solution was stirred at room temperature for 1 hr, then evaporated. To the residue was added H_2O and the solution was extracted with CH_2Cl_2. Evaporation of the sovent left brown crystals, which was recrystallized from aq. EtOH to give colorless plates (2.24 g, 48.5%), mp 111—112°. This compound was identified by the comparison of IR spectrum with that of XI obtained above.

4-Aminoalkyl-3-phenyl-, 4-Aminoalkyl-5-methyl-3-phenylisoxazoles (III), and Their Hydrochlorides——Nine compounds in Table II were prepared by the following general procedure and the bases obtained were converted to their hydrochlorides by the ordinary procedure. A solution of VII (0.01 mole) and amine (0.03 mole) in toluene (or EtOH) (20 ml) was heated at 110° for 10 hr (in a sealed tube if necessary), then cooled and acidified with 3% aq. HCl. The aq. phase was separated and the organic layer was extracted with H_2O. The combined aq. solution was made alkaline with 20% aq. NaOH and extracted with ether. Evaporation of the solvent gave, along with unreacted amine, the desired product (III),which was purified by distillation *in vacuo* or by recrystallization from petr. ether.

Reaction of IVa with NaOEt——To a solution of Na (0.46 g) in EtOH (20 ml) was added IVa (3.78 g) and the mixture was refluxed for 3 hr, then cooled, neutralized with AcOH and evaporated. To the residue was added H_2O and the solution was extracted with CH_2Cl_2. Evaporation of the solvent left a brown tar, which was chromatographed on alumina with benzene and subsequent $CHCl_3$ to give following products: benzonitrile (0.47 g, 22.9%) as lst fraction (benzene); 3-(α–aminobenzylidene)–2–tetrahydrofuranone (XIIa) (1.10 g, 29.5%) as 2nd fraction (benzene), which was recrystallized from benzene to give colorless needles, mp 150—151°. NMR τ (in $CDCl_3$): 2.57 (C_6H_5), 5.77, 7.18 (–CH_2CH–). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3512, 3360, 1696, 1629 (H_2N–C=C–COO–). *Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.58; H, 5.95; N, 7.82; and IVa as last fraction ($CHCl_3$), which was distilled *in vacuo* to give a colorless liquid (1.27 g, 33.5%).

Reaction of IVb with NaOEt——A solution of IVb (2.03 g) and Na (0.23 g) in EtOH (10 ml) was treated in a similar manner as the above to give following products: benzonitrile (0.23 g, 22.2%); 3-(α–amino-benzilidene)–2–tetrahydropyrone (XIIb) (0.59 g, 29.2%), which was recrystallized from benzene to give colorless prisms, mp 166—167°. NMR τ (in $CDCl_3$): 2.60 (C_6H_5); 5.77, 7.78, 8.23 (–$CH_2CH_2CH_2$–). IR $\tau_{max}^{CHCl_3}$ cm^{-1}: 3495, 3304, 1659, 1649 (H_2N–C=C–COO–). *Anal.* Calcd. for $C_{12}H_{13}O_2N$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.29; H, 6.56; N, 6.87; and VIb (0.84 g, 41.3%).

3-Amino-2-tetrahydrofuro[3,2-*d*]isoxazoline (XV)——To a solution of NaOH (0.4 g) and 12% aq. NaOCl (8 ml) was added IVe′ (1.56 g) portionwise with stirring and cooling in an ice–water bath and the resulting mixture was stirred at room temperature for 1 hr and then added dropwise into boiling H_2O (5 ml) with stirring. After reflux for 0.5 hr and then evaporation *in vacuo*, the residue was extracted with boiling EtOH and filtered. Evaporation of the solvent left colorless crystals, which was recrystallized from EtOH–benzene to give colorless plates (1.05 g, 82.1%), mp 156—157°. NMR τ (in D_2O): 3.98 (doublet, J=5.6 cps, O–CH–O). *Anal.* Calcd. for $C_5H_8O_2N_2$: C, 46.87; H, 6.29; N, 21.87. Found: C, 47.09; H, 6.41; N, 21.99. This compound afforded a picrate, which was recrystallized from $CHCl_3$ to give yellow prisms, mp 150—151°. *Anal.* Calcd. for $C_{11}H_{11}O_9N_5$: C, 36.98; H, 3.10; N, 19.62. Found: C, 37.04; H, 3.31; N, 19.60.

3-Amino-4-(3-hydroxypropyl)isoxazole (XVI)——A mixture of IVf′ (3.40 g), NaOH (0.8 g) and 12% aq. NaOCl (16 ml) was treated in a similar manner as the above to give yellow crystals (2.68 g, 94.4%). Recrystallization from AcOEt gave colorless prisms, mp 76—77°. NMR τ (in D_2O): 1.92 (triplet, $J=0.9$ cps, a proton at 5-position of isoxazole). *Anal.* Calcd. for $C_6H_{10}O_2N_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.82; H, 7.24; N, 19.84. This compound afforded an oxalate, which was recrystallized from EtOH–benzene to give colorless prisms, mp 116—117°. *Anal.* Calcd. for $C_8H_{12}O_6N_2$: C, 41.38; H, 5.21; N, 11.47. Found: C, 41.79; H, 5.59; N, 11.00.

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