Synthesis of Isoxazolium Salts Unsubstituted in the 3-Position

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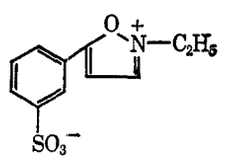
A variety of isoxazoles unsubstituted in the 3-position have been prepared and alkylated to form highly reactive isoxazolium salts, which are potentially useful as peptide bond-forming reagents. A few are inner salts related to Woodward's reagent K. The explosive nature of isoxazolium perchlorates is revealed.

Woodward and co-workers[1] have demonstrated that, like the well-known carbodiimides, isoxazolium salts which are unsubstituted in the 3-position serve as reagents for generation of a peptide bond. The reaction occurs under mild conditions between a protected amino acid or peptide and an amino acid ester or peptide ester. Such isoxazolium salts are also of interest as gelatin hardeners,[2] since the same reaction between pendant amino and carboxyl groups of adjacent gelatin chains results in cross-linking.

Woodward's group chose the *m*-sulfophenyl derivative **1** (commonly called Woodward's reagent K) as their specific reagent primarily because the *m*-sulfobenzoylacetamide formed as a by-product, being water-



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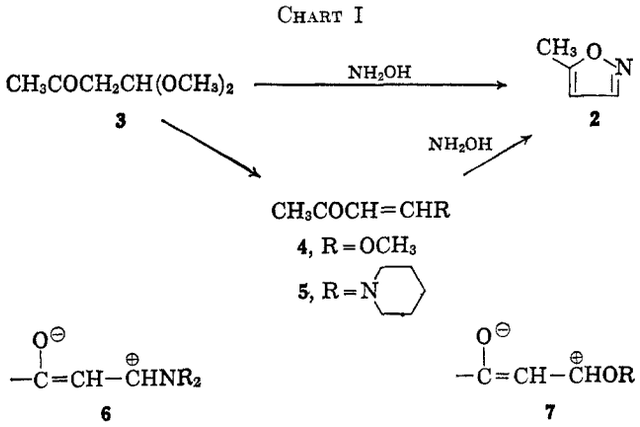
soluble, was readily separable from the peptide products. The lengthy synthesis of **1** was merely outlined by these workers. In general, the literature concerning isoxazolium salts is scant. Pertinent references include those cited by Woodward and Olofson;[3] in addition Lampe and Smolinska[4] have described the alkylation of 3,5-disubstituted isoxazoles.

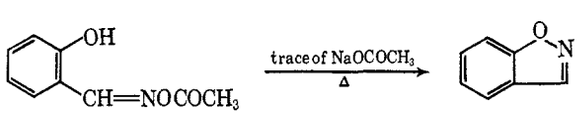
Our interest in these salts has led to an elaboration of the synthesis of **1** and an extension to several related inner salts. In addition, a variety of alkyl and arylisoxazolium salts of more facile synthesis have been prepared.

The synthesis of isoxazoles unsubstituted in the 3-position (by reaction of a β-ketoaldehyde or a β-dialdehyde with hydroxylamine) is complicated by several factors; among these are their instability to alkali (leading to the formation of β-ketonitriles),[5] and the lability of the requisite β-ketoaldehyde or β-dialdehyde intermediates, which prompts utilization of a more stable derivative, such as an acetal. Furthermore, the β-ketoaldehydes, being unsymmetrical, can lead to either 3- or 5-substituted isoxazoles or mixtures thereof. In order to form the 5 isomer preferentially, it is essential that hydroxylamine react with the aldehyde function (or its equivalent) more readily than with the keto group. This is best accomplished by means of a β-aminovinyl ketone intermediate (*e.g.*, **5**). In such a compound the greater stabilization (by nitrogen) of the important resonance contributor **6** compared to **7** (Chart I), for example, leads to attack by hydroxylamine almost exclusively in the β-position. Accordingly, 5-methylisoxazole (**2**) was prepared in good isomeric purity (>98%) from the readily available 4,4-dimethoxy-2-butanone (**3**) only by the indirect route **3** → **5** → **2** (Chart I). The direct route (**3** → **2**, Chart I) gave an approximate 1:1 mixture of 3- and 5-methylisoxazole, whereas the route *via* the ketovinyl ether (**3** → **4** → **2**) gave a 1:2 mixture. Other investigators[6] have reported that the corresponding ethyl ether gave the 3 isomer exclusively.

CHART I



Benz[*d*]isoxazole (**9**), prepared by the method of Lindemann and Thiele[7] from salicylaldoxime O'-acetate (**8**), was unobtainable unless a basic catalyst



(sodium acetate) was used in the pyrolysis. Without the catalyst salicylonitrile was formed, which, under the reaction conditions, trimerized to the known 2,4,6-tris(*o*-hydroxyphenyl)-*s*-triazine. Benz[*d*]isoxazole itself is thermally labile and undergoes a similar reaction upon prolonged heating.

Alkylation of the isoxazoles is complicated not only by their weakly basic nature but to a lesser degree also by the vulnerability of their quaternary salts to nucleophilic attack. It was usually advantageous to restrict reaction temperatures to 40–50°, which necessitated long reaction times with the common alkylating agents. Occasionally a higher reaction temperature

(1) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Am. Chem. Soc.*, **83**, 1010 (1961).

(2) Kodak Pathé S. A., French Patent 1,378,531 (1965).

(3) R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.*, **83**, 1007 (1961).

(4) W. Lampe and J. Smolinska, *Roczniki Chem.*, **28**, 163 (1954); **29**, 934 (1955); *Chem. Abstr.*, **49**, 8922 (1955); **50**, 10710 (1956).

(5) A. Quilico in "The Chemistry of Heterocyclic Compounds, Five- and Six-Membered Compounds with Nitrogen and Oxygen," A. Weissberger and R. H. Wiley, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, p 44.

(6) L. Panizzi and M. Sbrillo-Siena, *Gazz. Chim. Ital.*, **73**, 335 (1943); *Chem. Abstr.*, **41**, 1221 (1947).

(7) H. Lindemann and H. Thiele, *Ann.*, **449**, 63 (1926).

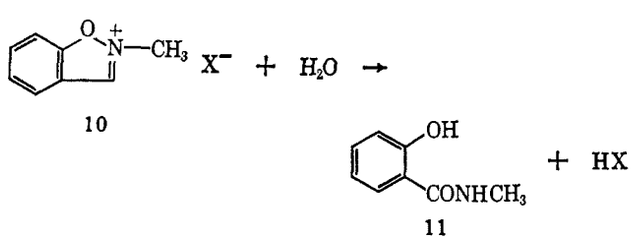
TABLE I
ISOXAZOLIUM SALTS

Compd	Method	R	R′	R″	X⁻	Yield,[a] %	M.p., °C	Formula	Calcd, % C	H	Cl	N	S	Found, % C	H	Cl	N	S
12	A	H	H	CH_3	PTS[b]	41	105–109	$C_{11}H_{13}NO_4S$	51.7	5.1	...	5.5	12.6	52.1	4.9	...	5.3	12.4
13	A	H	CH_3	CH_3	PTS	34	86–88	$C_{12}H_{15}NO_4S$	53.5	5.6	...	5.2	11.9	53.4	5.6	...	5.2	11.8
14a	A	CH_3	H	CH_3	PTS	80	111–112	$C_{12}H_{15}NO_4S$	53.5	5.6	...	5.2	11.9	53.8	5.7	...	4.9	11.8
14b	A	CH_3	H	CH_3	ClO_4[c]	64	92.5–95	$C_9H_8ClNO_5$	30.4	4.05	18.0	...	...	30.5	4.1	18.3	...	...
15	A[d]	$(CH_3)_2CH$	H	CH_3	ClO_4[c]	71	119–121	$C_7H_{10}ClNO_5$	37.3	5.4	15.7	6.2	...	37.5	5.4	16.0	6.3	...
16	A	H	$HO(CH_2)_3$	CH_3	PTS	20	Oil[e]	$C_{14}H_{19}NO_6S$	53.7	6.1	...	4.5	10.2	53.3	6.5	...	4.2	10.6
17	B	C_6H_5	H	CH_3	ClO_4[c]	59	180–181	$C_{10}H_{10}ClNO_5$	46.3	3.9	13.7	5.4	...	46.3	3.7	13.9	5.1	...
18	B	p-$CH_3C_6H_4$	H	CH_3	ClO_4[c]	54	166–167	$C_{11}H_{12}ClNO_5$	48.2	4.4	...	5.1	...	48.3	4.2	...	4.9	...
19	f	H	H	$(CH_2)_3SO_3^-$	(Inner salt)	82	Oil[g]	$C_6H_9NO_4S$	37.7	4.7	...	7.3	16.8	33.4	5.1	...	5.4	19.0
10	f	4,5-Benz derivative		CH_3	[h]	57	141–143	$C_{14}H_{11}N_3O_8S$	44.1	2.9	...	...	...	44.3	3.2	...	...	...
23	C	p-$ClSO_2C_6H_4$	H	C_2H_5	BF_4	88	88–89	$C_{11}H_{11}BClF_4NO_3S$	36.7	3.1	...	3.9	8.9	37.0	3.3	...	4.0	8.8
24	f	m-$ClSO_2C_6H_4$	H	C_2H_5	BF_4	87	161–162	$C_{11}H_{11}BClF_4NO_3S$	...	...	...	...	...	...	...	...	...	...
20	C	CH_3	H	C_2H_5	BF_4	71	39–40[i]	$C_6H_{10}BF_4NO$	36.1	5.0	...	7.0	...	36.3	5.1	...	6.8	...

[a] Yields are for purified products; crude yields ranged 20–50% higher. Recrystallization losses were due in part to hygroscopic products. [b] PTS is the *p*-toluenesulfonate anion. [c] This compound is highly impact sensitive. [d] Conditions of method A were used but with dimethyl sulfate as alkylating agent. [e] Purification of the noncrystalline salt was effected by repeated precipitation of its acetone solution in a large volume of ether. [f] See Experimental Section. [g] Analysis and infrared spectrum indicate possibly 25% 1,3-propanesultone as impurity. [h] X^- is the 2,4-dinitrobenzenesulfonate anion. [i] Hygroscopic product was recrystallized from 3:2 methanol–ethanol.

was necessary or a highly reactive reagent such as methyl 2,4-dinitrobenzenesulfonate or triethyloxonium fluoroborate was used. Hygroscopic or noncrystalline salts conveniently were converted to the nonhygroscopic perchlorates. Later it was found that the isoxazolium perchlorates are impact sensitive; a sample on a steel plate can be detonated by a mild blow of a hammer. This sensitivity is comparable to that of benzoyl peroxide. The perchlorates also decompose above their melting points and should be handled with due care.

Benz[*d*]isoxazole[7a] proved to be such a weak base that alkylation was not possible with methyl *p*-toluenesulfonate. Alkylation was effected in excellent yield, however, by using methyl 2,4-dinitrobenzenesulfonate.[8] The resulting benzisoxazolium salt **10** was found to be extremely sensitive to water, giving N-methylsalicylamide (**11**) in 85% yield. These results with **10** contrast sharply with the work of King and Durst[9] on 3-phenylbenzisoxazole. They found that alkylation



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with dimethyl sulfate gave a stable methosulfate salt which could be converted to the ferrichloride salt in aqueous solution. This notable difference in stability of the two benzisoxazolium salts correlates with the proposed mechanism of Woodward[3] for nucleophilic attack on isoxazolium salts, the first step depending on loss of the proton in the 3-position, possible only with **10**.

The syntheses of the 3-alkyl-5-arylisoxazoliumsulfonates (Table II) were undertaken to find a more economical route to the type of compound exemplified by **1**. The 5-*p*-tolyl homolog **28** can be prepared without the troublesome, yield-lowering isomeric mixtures encountered with **1**. (In the chlorosulfonation of 5-phenylisoxazole a mixture of the 3′-chlorosulfonyl and 4′-chlorosulfonyl compounds is obtained. This is not possible with 5-*p*-tolylisoxazole.) The anticipated advantages were realized when an over-all yield, from the 5-arylisoxazole intermediate, of 41% for **28** was obtained as compared with 18% for **1**. The alkylation of 5-(3-chlorosulfonyl-*p*-tolyl)isoxazole was effected with dimethyl sulfate, and the resulting product was converted without isolation to the inner salt. In the synthesis of **1**, the Woodward procedure involved alkylation of the mixed isomers, 5-(3- and 4-chlorosulfonylphenyl)isoxazole, with triethyloxonium fluoroborate and separation of the resulting isoxazolium salts before the final hydrolysis step. The undesired isomer (**25**) is the less soluble of the isomeric inner salts, and accordingly is difficult to remove in the final stage.

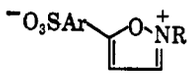
(7a) NOTE ADDED IN PROOF.—A study of the preparation and properties of the N-ethylbenzisoxazolium cation has just been published by D. S. Kemp and R. B. Woodward, *Tetrahedron*, **21**, 3019 (1965).

(8) A. I. Kiprianov and A. A. Tolmachev, *J. Gen. Chem. USSR*, **27**, 553 (1957); **29**, 2828 (1959).

(9) J. F. King and T. Durst, *Can. J. Chem.*, **40**, 882 (1962).

TABLE II

2-ALKYL-5-ARYLISOXAZOLIUM SULFONATES

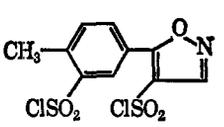


Compd	R	^-O_3SAr	Mp, °C[a]	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
1	C_2H_5	m-$C_6H_4SO_3^-$	209.5–211 dec[b]	$C_{11}H_{11}NO_4S$	...	...	...	...	...	...	...	...
25	C_2H_5	p-$C_6H_4SO_3^-$	198.5 dec	$C_{11}H_{11}NO_4S \cdot 0.5H_2O$	50.4	4.5	5.4	12.2	50.8 50.5	4.5 4.4	5.4	12.8
26	CH_3	m-$C_6H_4SO_3^-$	206.5–207.5 dec	$C_{10}H_9NO_4S \cdot 0.5H_2O$	48.5	4.0	5.8	...	48.2 48.0	4.2 3.8	5.8	...
27	CH_3	p-$C_6H_4SO_3^-$	214–215 dec	$C_{10}H_9NO_4S \cdot H_2O$	46.7	4.3	5.45	12.4	46.6 46.7	4.4 4.3	5.7	...
28	CH_3	4-CH_3-3-$SO_3C_6H_3^-$	232–235 dec	$C_{11}H_{11}NO_4S$	52.1	4.3	5.5	...	51.9	4.3	5.3	...

[a] Bath was preheated to 10–15° below the melting point. [b] Woodward, *et al.*,[3] reported mp 207–208° dec.

The chlorosulfonylphenylisoxazoles of Woodward were also alkylated with dimethyl sulfate and hydrolyzed without separation, to give a mixture of the inner salts **26** and **27**. These were separated at this final step, and it was found that the relative water solubilities are advantageously reversed from those of the 2-ethyl compounds.[10]

It should be pointed out that in the chlorosulfonation of 5-*p*-tolylisoxazole, careful control of temperature is required to avoid formation of the 3′,4-bis(chlorosulfonyl) derivative **21**.



21

The isoxazolium salts prepared are listed in Tables I and II.

Experimental Section

All melting points are corrected. Commercial materials were used as received.

A. Syntheses of 3-Unsubstituted Isoxazoles. Isoxazole was prepared from 1,1,3,3-tetraethoxypropane and aqueous hydroxylamine hydrochloride, separated from the ethanol azeotrope by precipitation with cadmium chloride,[11] regenerated from the complex by steam distillation, and purified in a normal manner: bp 94° (746 mm), $n^{25}D$ 1.4250; lit.[12] bp 95°, $n^{25}D$ 1.4216.

4-Methylisoxazole.—Allyl ethyl ether was isomerized in an unknown but poor conversion to ethyl propenyl ether by the method of Price and Snyder.[13] The distillate, containing a mixture of the two isomers, was allowed to react with excess ethyl orthoformate by the procedure of Zeller, *et al.*,[14] to give 2-methyl-1,1,3,3-tetraethoxypropane: bp 90–92° (7 mm), $n^{25}D$ 1.4122; lit.[15] bp 98.5–100° (8 mm), $n^{20}D$ 1.4138. This was converted to 4-methylisoxazole in a manner similar to isoxazole above: bp 126.5–127° (743 mm), $n^{25}D$ 1.4357; lit.[16] bp 126–127°, $n^{20}D$ 1.4355.

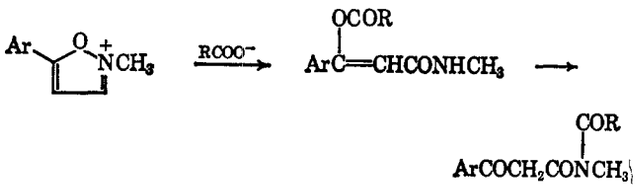
5-Methylisoxazole (2). 1. From 4,4-Dimethoxy-2-butanone (3).—To a stirred solution of 139 g (2.0 moles) of hydroxylamine hydrochloride and 5 ml of concentrated hydrochloric acid in 300 ml of water was added 264 g (2.0 moles) of 4,4-dimethoxy-2-butanone. When the moderately exothermic reaction had subsided, methanol was distilled with a short packed column, the head temperature being kept below 85°. (The distillate will become turbid if methylisoxazole distils.) When all the methanol had been removed, the residue was neutralized to pH 7–8 and the isoxazole was extracted with dichloromethane, dried over magnesium sulfate, and fractionally distilled to give the methylisoxazole in several fractions, boiling in the range 119–121°. By nmr analysis, the various fractions were shown to contain from 48 to 78% of the 5 isomer; the over-all ratio was calculated to be about 55% 5 isomer.

2. From 4-Methoxy-3-buten-2-one (4).—Similarly, the methylisoxazole product was about 70% 5 isomer.

3. From 4-Piperidino-3-buten-2-one (5).—A mixture of 182 g (1.38 moles) of 4,4-dimethoxy-2-butanone, 250 ml of dry piperidine, 700 ml of benzene, and 6 g of *p*-toluenesulfonic acid was distilled with a packed column, the head temperture being controlled to 75° by adjusting the reflux ratio. When it was no longer possible to keep the temperature below 75° (5–10 hr), the volatiles were removed *in vacuo* and the residue was distilled to give 125 g (59%) of 4-piperidino-3-buten-2-one as a viscous, pale yellow oil: bp 87–90° (0.08–0.09 mm), $n^{25}D$ 1.5713; lit.[17] bp 154–157° (7 mm), $n^{20}D$ 1.5730. A solution of 62.6 g (0.900 mole) of hydroxylamine hydrochloride in 125 ml of water was added to 125 g (0.816 mole) of 4-piperidino-3-buten-2-one at such a rate that the temperature was maintained under control. When addition was complete, the mixture was heated on the steam bath for 2 hr, cooled, neutralized to pH 7.2, extracted with dichloromethane, etc., to give 55 g (81%) of 5-methylisoxazole: bp 120–121° (748 mm), $n^{25}D$ 1.4364; lit.[18] bp 121–122° (750 mm), $n^{20}D$ 1.4368. By nmr analysis it contained less than 2% of the 3 isomer.

5-Isopropylisoxazole.—A large sample of 5-isopropylisoxazole from the Tennessee Eastman Research Laboratories is gratefully acknowledged. It was prepared from 1-dimethylamino-4-

(10) Although **26** might appear to present some advantage over **1** from the synthetic standpoint, a dissertation (R. A. Olofson, Ph.D. Thesis, Harvard University, 1961), which has been called to our attention by a referee, discloses that the N-methylisoxazolium salts such as **26** are inferior to the N-ethyl homologs in peptide synthesis because of the instability of the active esters formed in their reaction with the carboxylate anion. Acyl migration gradually occurs to form a diacylimide. The N-ethyl radical,



on the other hand, has sufficient steric influence to inhibit this rearrangement.

(11) L. Claisen, *Ber.*, **36**, 3664 (1903).

(12) G. Speroni and P. Pino, *Gazz. Chim. Ital.*, **80**, 549 (1950); *Chem. Abstr.*, **45**, 7107 (1951).

(13) C. C. Price and W. H. Snyder, *J. Am. Chem. Soc.*, **83**, 1773 (1961).

(14) P. Zeller, *et al.*, *Helv. Chim. Acta*, **42**, 841 (1959).

(15) I. N. Nazarov, S. M. Makin, and B. K. Kruptsov, *J. Gen. Chem. USSR*, **29**, 3641 (1959).

(16) P. Pino and R. Ercoli, *Gazz. Chim. Ital.*, **81**, 757 (1951); *Chem. Abstr.*, **46**, 7042 (1952).

(17) N. K. Kochetkov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 883 (1953).

(18) N. K. Kochethov, *ibid.*, 37 (1954).

methyl-1-penten-3-one, available from the reaction of ketene with N,N-dimethylisobutenylamine.[19]

4-(3-Hydroxypropyl)isoxazole.—A mixture of 116 g of 3-diethoxymethyl-2-ethoxytetrahydropyran,[20] 100 ml of water, and 1 ml of glacial acetic acid was boiled, and ethanol was removed through a short column with a variable-reflux still head. After 70 ml of distillate had been removed, an additional 50 ml of water and 1 ml of acetic acid were added and distillation was continued to a head temperature of 90°. The resulting solution of 3-hydroxypropylmalonaldehyde was mixed with a solution of 35 g of hydroxylamine hydrochloride in 50 ml of water, and followed by treatment as in method 3 for 5-methylisoxazole, to give 50.4 g of 4-(3-hydroxypropyl)isoxazole, bp 78–82° (0.03–0.05 mm), $n^{25}D$ 1.4791, over-all yield 79%.

Anal. Calcd for $C_6H_9NO_2$: C, 56.7; H, 7.1; N, 11.0; mol wt, 127. Found: C, 55.7; H, 7.0; N, 10.9; mol wt, 130 (thermometric in acetone).

5-Phenylisoxazole was prepared from 3-dimethylaminoacrylophenone[21] in 89% yield, as described in method 3 for 5-methylisoxazole: bp 60–84° (0.07–0.09 mm), mp 21–22°, $n^{25}D$ 1.5832; lit.[22] mp 22–23°.

5-*p*-Tolylisoxazole.—3-Dimethylamino-4′-methylacrylophenone was prepared in 50% yield by the method of Benary:[21] mp 97–97.5° from benzene–ligroin (bp 66–75°) (*ca.* 1:4).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.2; H, 8.0; N, 7.4. Found: C, 76.0; H, 8.2; N, 7.3.

Conversion to the isoxazole was accomplished in 56% yield: mp 59–60°, lit.[23] mp 60°. The structure of the product was confirmed by a favorable comparison of its nmr spectrum with that of the known 5-phenyl compound.

Benzisoxazole (9).—Essentially the procedure of Lindemann and Thiele[7] was used. Recrystallized salicylaldoxime O′-acetate (**8**), when carefully heated alone at 120–140° under aspirator vacuum (11 mm), gave a small amount of distillate, consisting mostly of acetic acid and some salicylonitrile (determined by the presence of a nitrile band in the infrared spectrum). The bulk of the material remained as a yellow solid in the flask (in 99% crude yield). Several recrystallizations from 2-butanone gave 2,4,6-tris(*o*-hydroxyphenyl)-*s*-triazine as pale yellow crystals: mp 308–311°, lit.[24] mp 307–309°.

Recrystallized **8** (55.2 g, 0.308 mole) and 0.12 g of sodium acetate were melted together on the steam pot under aspirator vacuum (11 mm). The distillate (208 g) was collected over a period of several hours. The pressure was then reduced to 3.3 mm and distillation proceeded at about 63°. After some 15 g had been collected, the temperature suddenly rose sharply and salicyclonitrile began crystallizing in the condenser. The two fractions of **9** were combined and redistilled. After a forerun of acetic acid, 21 g (57%) yield) of benzisoxazole distilled as a clear oil: bp 64–67° (3.5 mm), $n^{25}D$ 1.5589; lit. bp 82–83° (14 mm),[7] $n^{20}D$ 1.5616.[25]

B. Isoxazolium Salts (Table I). Method A.—A solution of the isoxazole and a 50% excess of methyl *p*-toluenesulfonate in an equal volume of acetonitrile was heated at 40–50° for a period of 2–10 days in a stoppered flask. The solvent was removed *in vacuo* and the residual oil or solid was washed thoroughly with ether. The crude product was recrystallized from an appropriate solvent (acetone or acetone–ether) or converted to the perchlorate salt. For water-insoluble perchlorates, concentrated aqueous sodium perchlorate was used; otherwise (*e.g.*, **14b**), acetonitrile was employed. The desired perchlorate salt was isolated after removal of the precipitated sodium tosylate and recrystallized from methanol or water.

Method B.—A mixture of the isoxazole and 100% excess of dimethyl sulfate was heated in a closed flask at 70–75° for 3 days and cooled. Ether was added and the precipitated oil was washed well with ether and treated subsequently as in method A.

Method C.—A solution of the isoxazole and an approximately equivalent amount of triethyloxonium fluoroborate[26] in dry methylene chloride was stirred at 25° for several hours. The solvent was removed, if necessary, and the product was recrystallized from ethyl acetate, acetonitrile, or acetone–ether.

3-(2-Isoxazolium)propanesulfonate (19).—A mixture of 3.45 g of isoxazole and 10 g of 1,3-propanesultone in a stoppered flask was heated for 1 day at 45°, then for 1 day at 75°. Benzene was used to dilute the viscous mass and to remove much of the excess sultone. The oil layer was purified by repeated solution in methanol and precipitation by pouring slowly into stirred benzene. The resulting oil was then dried to give 7.88 g (82%) of **19** as a yellow, viscous oil. The infrared spectrum of this oil indicated the presence of unreacted sultone.

Anal. Calcd for $C_6H_9NO_4S$: C, 37.7; H, 4.7; N, 7.3; S, 16.8. Calcd for 75% product and 25% 1,3-propanesultone: C, 35.6; H, 4.8; N, 5.5; S, 19.2. Found: C, 33.4; H, 5.1; N, 5.4, 5.3; S, 19.0.

N-Methylbenzisoxazolium 2,4-Dinitrobenzenesulfonate (10).—A solution of 2.38 g (0.020 mole) of benz[*d*]isoxazole (**9**) and 4.92 g (0.019 mole) of methyl 2,4-dinitrobenzenesulfonate[8] in 25 ml of acetonitrile in a stoppered flask was heated in a constant-temperature bath at 40° for 12 days. The volatiles were removed under vacuum and the residue was shaken with benzene, decanted, and shaken wth several portions of ether before the oil would crystallize. The precipitate was collected, washed with ether, and dried to give 6.55 g (91%) of crude benzisoxazolium salt. Several recrystallizations from acetone–ether gave nearly colorless crystals of **10**, mp 141–143°.

Benz[*d*]isoxazole was recovered from a similar attempt at alkylation with dimethyl sulfate.

Attempted Conversion to N-Methylbenzisoxazolium Perchlorate.—To a solution of 4.05 g (0.0106 mole) of **10** in 100 ml of acetone was added, dropwise over several minutes, with stirring, 0.0106 mole of a standardized solution of hydrated sodium perchlorate in acetone. The precipitate of sodium 2,4-dinitrobenzenesulfonate was removed and the filtrate was concentrated under vacuum. The residue (4.23 g) was recrystallized twice from water (using a seed crystal) to give 1.04 g of colorless crystals of N-methylsalicylamide, mp 84–86°.

Anal. Calcd for $C_8H_9NO_2$: C, 63.6; H, 6.0; N, 9.3. Found: C, 63.4; H, 5.8; N, 9.1.

The literature[27] gives mp 89° for N-methylsalicylamide.

C. Chlorosulfonation of 5-Arylisoxazoles and Conversion to Isoxazolium Inner Salts (Table II). 5-(3- and 4-Chlorosulfonylphenyl)isoxazoles. 1.—A solution of 79 g (0.54 mole) of 5-phenylisoxazole and 194 g (1.66 moles) of distilled chlorosulfonic acid was heated at 100–113° for 24 hr, cooled, and poured onto crushed ice. The crude crystalline solid was isolated in low yield (40 g), indicating incomplete reaction. Fractional crystallization from benzene–ligroin produced 3.9 g of colorless 5-(4-chlorosulfonylphenyl)isoxazole[28] (**22**), mp 147.5–148.5° (from carbon tetrachloride), and 10.5 g of the 2:1 inseparable mixture of 3′- and 4′-chlorosulfonyl compounds, mp 90–92° (from carbon tetrachloride), reported by Woodward, *et al.*,[3] to melt at 92.6–92.8°.

Anal. Calcd for $C_9H_6ClNO_3S$: C, 44.4; H, 2.5; Cl, 14.7; S, 13.1. Found (4′ isomer): C, 44.2; H, 2.5; Cl, 15.3; S, 12.8. Found (mixed isomers): C, 44.0; H, 2.4; Cl, 15.2; S, 13.1.

2.—A similar reaction with a 5:1 molar ratio of chlorosulfonic acid to the isoxazole and heating at 102–114° for 29 hr produced a 58% crude yield of products from which a 40% yield of the 2:1 molecular compound was obtained.

5-(3- and 4-Chlorosulfonylphenyl)-2-ethylisoxazolium Fluoroborate (24 and 23).—A solution of 101 g (0.415 mole) of the 2:1 molecular compound from the chlorosulfonation reaction and 79 g (0.415 mole) of triethyloxonium fluoroborate in 250 ml of dry methylene chloride was heated under reflux for 3 hr. The colorless crystals (86 g) which separated on standing were nearly pure 3′ isomer, mp 158–161.5°. Recrystallization from acetone–ether raised the melting point to 161–162°, as reported by Woodward, *et al.*[3] The over-all yield from 5-phenylisoxazole was 18%.

Evaporation of the original filtrate and recrystallization of the residue from acetone–ether yielded 43 g of impure 4′ isomer **23**, mp 81.5–89°, not improved by further recrystallization. The pure salt was obtained, however, from the pure base (**22**).

2-Ethyl-5-phenylisoxazolium 4′-Sulfonate (25).—A suspension of 30 g of the impure **23** of the preceding section in 200 ml of 25% aqueous ethanol was stirred at 25° for 18 hr and filtered: yield, 14.2 g; mp 198.5 dec. This, together with a second crop

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of 2.7 g, was recrystallized from 150 ml of water to give 12.5 g of colorless platelets of **25** with unchanged melting point. The 4′-position of the sulfonate group was confirmed by the nmr spectrum. Unlike the 3′ isomer, **25** is quite insoluble in cold water.

2-Ethyl-5-phenylisoxazolium 3′-Sulfonate (1).—A suspension of 78.2 g of **24** in a solution consisting of 400 ml of ethanol, 100 ml of water, and 100 ml of hydrochloric acid (*d* 1.19) was stirred at 25° for 16 hr. The resulting clear solution was concentrated to 200 ml in a 35° bath, and 1800 ml of ethanol was added. The crude, colorless crystals which separated on cooling were recrystallized from dilute ethanol to give 43 g (78% yield) of fine crystals.

2-Methyl-5-phenylisoxazolium 3′- and 4′-Sulfonates (26 and 27).—A solution of 5.0 g of the 2:1 mixture of 5-(3- and 4-chlorosulfonylphenyl)isoxazole and 5 ml of dimethyl sulfate in 10 ml of acetonitrile was held at 40° for 70 hr, and the solvent was evaporated. The residual oil was washed with ether and hydrolyzed in 6.5 ml of water and 10 ml of ethanol during 18 hr at 25°. By fractional crystallization from water and dilute ethanol were isolated 1.35 g of the less soluble 3′ isomer **26** from water and 0.55 g of the more soluble 4′ isomer (**27**) from dilute ethanol. The positions of the anionic sulfonate substituent were determined by comparison of the infrared and nmr spectra with those of the known 2-ethyl homologs. It is interesting to note that the solubilities of the 3′ and 4′ isomers in the two sets (methyl and ethyl) are reversed.

5-(3-Chlorosulfonyl-*p*-tolyl)isoxazole. A.—A solution of 16 g (0.1 mole) of 5-*p*-tolylisoxazole and 59 g (0.5 mole) of distilled chlorosulfonic acid was held at 20–25° for 24 hr, protected from the atmosphere by a tube of Drierite. Essentially no reaction occurred at this temperature; therefore, the temperature of the solution was raised, with stirring, to 58–60° (HCl evolution) and held there for 18 hr. The solution was cooled and poured into ice, and the yellow solid which separated was filtered, washed with cold water, and dissolved in chloroform. The chloroform solution, after drying over magnesium sulfate, followed by a charcoal treatment, yielded 19 g (74%) of crude product on evaporation. Recrystallization from 300 ml of carbon tetrachloride produced 16.8 g (65%) yield) of pure, cream-colored plates, mp 140–142°. An analytical sample melted at 141–142.5°.

Anal. Calcd for $C_{10}H_8ClNO_3S$: C, 46.6; H, 3.1; Cl, 13.8. Found: C, 46.6; H, 3.2; Cl, 14.0.

B.—In a similar, earlier run in which the temperature was held at 25° for 2 hr, followed by 73–75° for 24 hr, only a 10% yield of the sulfonyl chloride was obtained from chloroform extracts of the drowned reaction mixture. A second fraction (*ca.* 7% yield) was isolated from the carbon tetrachloride recrystallization filtrates. This, after several recrystallizations (methylcyclohexane), melted at 93–98° and was indicated by its infrared spectrum and elemental analysis to be largely a di(chlorosulfonyl) derivative of 5-*p*-tolylisoxazole contaminated with the monosubstituted compound.

The aqueous solution from the chloroform extraction was treated with an aqueous solution containing 364 g of barium acetate. After removal of the precipitated barium sulfate from the hot aqueous solution, 59 g of a crystalline, white solid separated on cooling. Another 29.5 g was obtained on further treatment of the filtrate with 50 g of barium acetate. Recrystallization from water gave 66 g of what was judged by the nmr spectrum to be the pure barium salt of 5-*p*-tolylisoxazole-3′,4-disulfonic acid.

Anal. Calcd for $C_{10}H_7BaNO_7S_2$: C, 26.4; H, 1.5; Ba, 30.1; N, 3.1; S, 14.1. Found: C, 26.4; H, 1.7; Ba, 30.1; N, 2.8; S, 13.8.

2-Methyl-5-*p*-tolylisoxazolium 3′-Sulfonate (28).—By a procedure similar to that employed for **26** and **27**, a 63% yield of this product was obtained with recrystallization from dilute ethanol. The over-all yield from 5-*p*-tolylisoxazole was 41%. The 3′-position of the sulfonate substituent was indicated by the nmr spectrum.

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An Unusual Stevens Rearrangement of a Tetrahydropyridinium Salt

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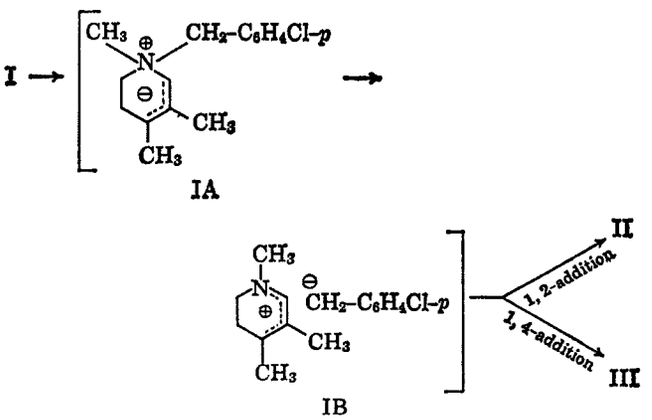
In the presence of ethereal phenyllithium, 1,3,4-trimethyl-1-*p*-chlorobenzyl-1,2,5,6-tetrahydropyridinium chloride (I) undergoes rearrangement to the expected product, 1,3,4-trimethyl-2-*p*-chlorobenzyl-1,2,5,6-tetrahydropyridine (II) in about 15% yield, and to two other products, 1,3,4-trimethyl-4-*p*-chlorobenzyl-1,4,5,6-tetrahydropyridine (III), and 1,3,3-trimethyl-2-*p*-chlorophenyl-4-methylenepiperidine (IV). Their structures have been proven by infrared, pmr, and mass spectral data. Possible routes for these rearrangements are discussed.

1,3,4-Trimethyl-1-*p*-chlorobenzyl-1,2,5,6-tetrahydropyridinium chloride (I) was prepared because it was expected to yield 1,3,4-trimethyl-2-*p*-chlorobenzyl-1,2,5,6-tetrahydropyridine (II) under Stevens rearrangement conditions.[1] Compound II was desired as a precursor for the benzomorphan structure V, which was considered interesting for testing as an analgesic.[2]

The pyridinium salt I was subjected to Stevens rearrangement conditions with phenyllithium, and the biphasic mixture was worked up in the usual way. A glpc of the product showed that it was a mixture of three main components, in the ratio 2:1:2. The product was distilled through a spinning-band column, and the three fractions which were collected were further purified by repeated recrystallization of their picrates. Microanalysis showed that the three compounds were isomers, with the formula $C_{15}H_{20}ClN$ (free base). One of these isomers, the intermediate fraction obtained from the distillation, was the expected



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