Tetrahedron, 1965, Vol. 21, pp. 3019 to 3035. Pergamon Press Ltd. Printed in Northern Ireland

THE N-ETHYLBENZISOXAZOLIUM CATION—I

PREPARATION AND REACTIONS WITH NUCLEOPHILIC SPECIES

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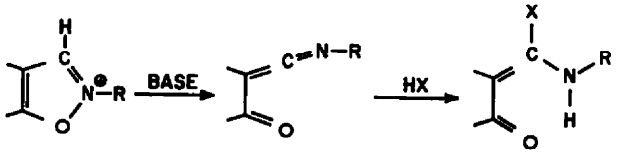
(*Received* 8 *May* 1965)

Abstract—The preparation and properties of the N-ethylbenzisoxazolium cation are described. The cation is shown to react rapidly in aqueous solution with a wide variety of nucleophiles, yielding *o*-hydroxy-N-ethylbenzimido derivatives. With carboxylate, cyanate, or thiocyanate anions, or with thiourea, internal rearrangements occur, converting the imido adducts to O-substituted products. The reactions of N-alkylated benzisoxazoles generate a broad spectrum of unusual substances which are obtainable with difficulty by other routes and which may serve as starting materials for the synthesis of many hitherto-inaccessible systems.

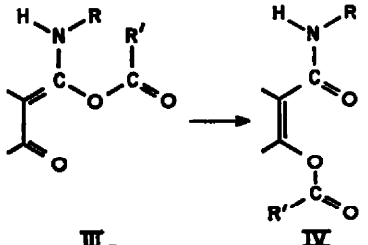
INTRODUCTION

WOODWARD and Olofson in 1961 described their re-examination of the chemistry of Mumm's isoxazolium salts and demonstrated the intermediacy of ketoketenimines in the reactions of these substances.[1] In a further publication Woodward *et al.* applied



I II III

the reaction of carboxylate anions with isoxazolium salts to the chemical synthesis of peptides.[2] The initial product (IIIa) of the reaction of a ketoketenimine (II) with a carboxylic acid rearranges very rapidly to form an enol ester (IV) which can be employed as an acylating agent.

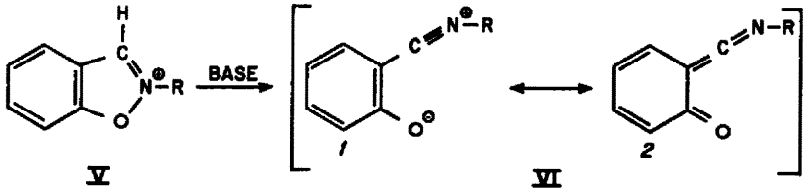


IIIa IV

X=R'–C(=O)–O⊖

[1] R. B. Woodward and R. A. Olofson, *J. Amer. Chem. Soc.* **83**, 1007 (1961).
[2] R. B. Woodward, R. A. Olofson and H. Mayer, *J. Amer. Chem. Soc.* **83**, 1010 (1961).

Although previous workers have studied only 2,4,5-trisubstituted isoxazolium salts, these remarkable transformations should occur with any derivative of an isoxazolium salt which bears a proton on its *three* position. The N-alkylbenzisoxazolium cations (V) are obvious choices for further study of the isoxazole cleavage, for by stabilizing a 4,5 double bond, benzo-fusion would be expected to change the properties of all isoxazole-derived intermediates and products. To take an example, the benzoketoketenimine (VI) should possess enhanced polar character due to the



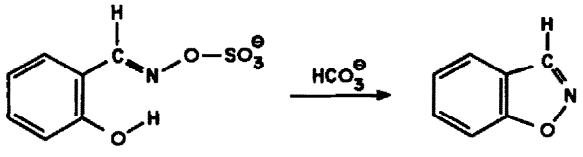
V VI

contribution of structure VI_1, and accordingly should be more reactive than ketoketenimines derived from simple isoxazolium salts.

Although the first benzisoxazole was prepared by Victor Meyer in 1892,[3] and N-alkylated benzisoxazolium salts bearing 3-aryl substituents were described in 1931 by Kohler,[4] simple N-alkylated derivatives of benzisoxazole have not been reported. In this communication we describe a convenient preparation of N-ethylbenzisoxazolium fluoborate and discuss the reactions of this substance with a variety of nucleophiles. Subsequent articles in this series will consider in turn the mechanism of these reactions and the utility of the N-ethylbenzisoxazolium cation for the synthesis of peptides.

Synthesis and general properties of the N-*ethylbenzisoxazolium cation*

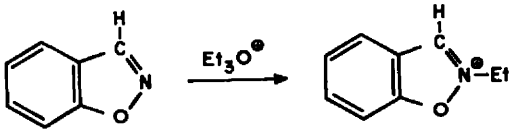
Although benzisoxazole has been prepared by pyrolysis of salicylaldoxime acetate[5] and by alkaline decomposition of salicylaldoxime carbamate,[6] neither procedure is suited to large-scale synthesis. A more satisfactory approach utilizes the oxime O-sulphonate of salicylaldehyde described by Sommer.[7] When salicylaldehyde is combined in aqueous solution with hydroxylammonium O-sulphonate, the soluble oxime O-sulphonate(VII)is formed. Treatment of the resulting solution with mild base releases benzisoxazole in a yield of 95%. This procedure has been applied successfully to a variety of salicylaldehydes and appears to be generally suited to the preparation of benzisoxazoles.



VII VIII

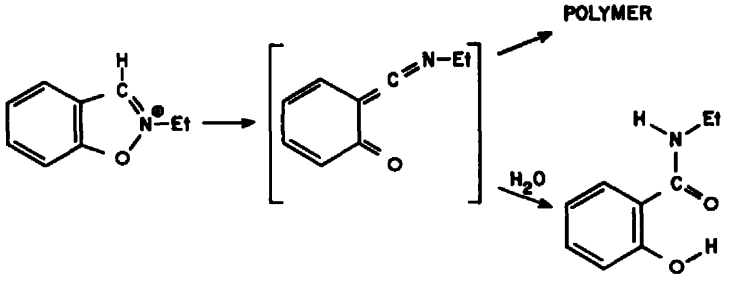
[3] W. R. Cathcart and V. Meyer, *Ber. Dtsch. Chem. Ges.* **25**, 3291 (1892).
[4] E. P. Kohler and W. F. Bruce, *J. Amer. Chem. Soc.* **53**, 644 (1931).
[5] H. Lindemann and H. Thiele, *Liebigs Ann.* **449**, 63 (1926).
[6] A. Conduché, *Ann. Chim.* [8], **13**, 46 (1908); O. Exner, *Coll. Czech. Chem. Comm.* **22**, 335 (1957).
[7] F. Sommer, O. F. Schulz and M. Nassau, *Z. Anorg. u. Allgem. Chem.* **147**, 145 (1925).

Benzisoxazole is too weakly nucleophilic and too heat-sensitive to combine with the common alkylating agents, but reaction with Meerwein's triethyloxonium fluoborate[8] occurs at room temperature in dichloromethane solution to generate a single substance of empirical formula $C_9H_{10}NOBF_4$ in essentially quantitative yield. When this salt is heated for several hours at 80° in hydrochloric acid solution it is converted in high yield to N-ethylsalicylamide, a result which establishes the alkylation product as the desired N-ethylbenzisoxazolium fluoborate (Va).



VIII Va R=Et

The salient features of the chemistry of Va quickly emerged. The decomposition of the substance is catalyzed by bases; aqueous solutions of it are stable for many hours at pH 1, they decompose within minutes at pH 4, and the substance disappears within the time of dissolution at pH 7. In the absence of reactive anions, the final product of the decomposition is N-ethylsalicylamide (IXa') although at pH's greater than 7 increasing quantities of a yellow, uncharacterized by-product are formed. A similar product is obtained when a solution of the salt in a neutral organic solvent is treated with an equivalent of triethylamine. Both materials appear to be inhomogeneous and to contain components of high mol. wt.



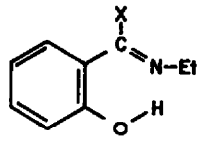
Va VIa R=Et IXa'

Although these results are in accord with a reaction sequence involving formation of the benzoketoketenimine (VIa), efforts directed toward direct observation of this substance failed. Even in dichloromethane solution at −50°, Va reacts with triethylamine to yield yellow, polymeric materials as the first observable products. From these experiments it is clear that the mechanism of decomposition of Va cannot be resolved by direct methods. Kinetic evidence which demonstrates the intermediacy of the benzoketoketenimine in these reactions will be presented in a subsequent publication.

Products with simple nucleophiles

Addition of the N-ethylbenzisoxazolium cation to aqueous solutions of hydrosulphide, fluoride, or cyanide, or to a methanol solution of methoxide generates high

[8] H. Meerwein, E. Battenberg, H. Gold, E. Pfeil and G. Willfang, *J. Prakt. Chem.* **154**, 83 (1939).



a, X=OH
b, SH
c, F
d, CN
e, OMe

IX

yields of products to which the general formula IX can be assigned. The proofs of structure rest on the chemical transformations summarized in Chart I and on spectroscopic evidence. Particularly noteworthy among the latter is the presence of low-field resonance at ca.—2τ in the NMR spectra of the methoxide, fluoride and cyanide products which is attributable to strongly hydrogen-bonded protons. It is of some interest that the methylene resonance of the hydrosulphide product appears as a quintet, implying that this substance exists predominantly as its thioamide tautomer (IXb′).

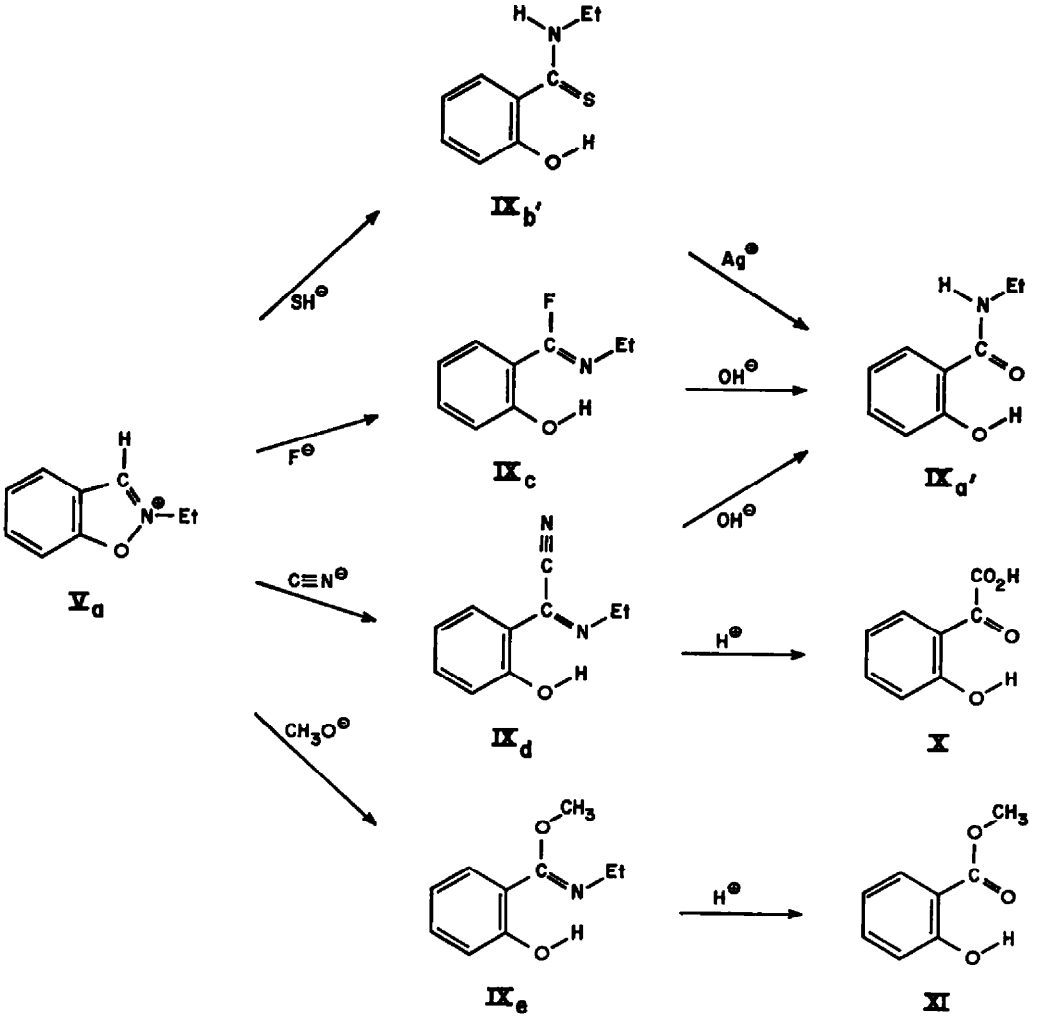
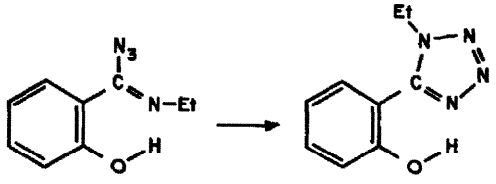


CHART I

Reaction of the benzisoxazolium cation with a cold, aqueous solution of azide ion buffered at pH 3 generates an unstable yellow oil whose infrared spectrum shows strong azide absorption at 4·7 μ. In inert solvents at room temperature the oil changes within minutes to a white, crystalline solid of empirical formula $C_9H_{10}N_4O$, whose

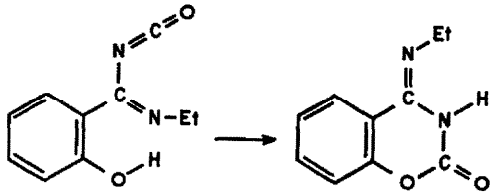


IXf XII

physical properties are in accord with its formulation as 1-ethyl-2-(2-hydroxyphenyl)-tetrazole (XII). The yellow precursor may be regarded as an imidoazide (IXf) and the isomerization as an intramolecular 1,3-dipolar addition analogous to that observed by Olofson and Woodward for an imidoazide derived from a simple isoxazolium salt.[1]

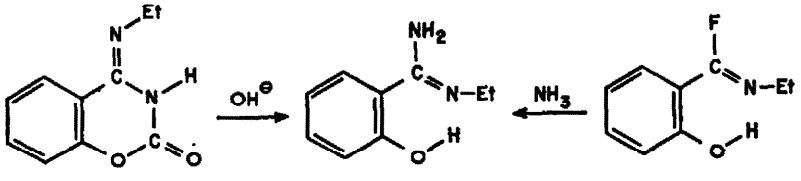
Products derived from cyanate, thiocyanate and carboxylate anions

The imidoisocyanate (IXg) which by analogy with the above results is the expected product of the reaction of the benzisoxazolium cation with cyanate ion, would be



IXg XIII

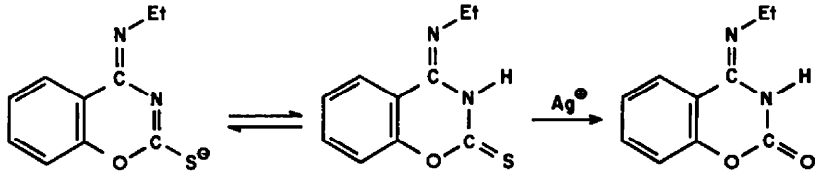
expected to undergo an internal condensation to form a cyclic urethane (XIII). That the latter structure in fact corresponds to the product of the reaction follows from the following observations. The cyanate product, empirical formula $C_{10}H_{10}N_2O_2$, shows strong IR carbonyl absorption at 5·79 μ and 6·18 μ, and contact with strong sodium hydroxide solution saponifies the substance to the amidine (IXh) obtained independently by reaction of IXc with ammonium hydroxide.



XIII IXh IXc

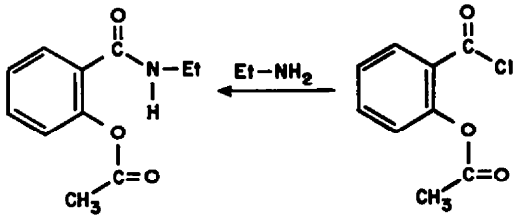
Reaction of the benzisoxazolium salt with thiocyanate ion generates a substance of empirical formula $C_{10}H_{10}N_2OS$, whose NMR spectrum is nearly identical with that of the cyanate product. The absence of 5·79 μ absorption in the IR spectrum of the

thiocyanate product suggests that it differs from the cyanate product only in the functionality of a single carbonyl group. The observation that acidic silver nitrate solution converts the thiocyanate product to the cyanate product, together with the fact that the thiocyanate product undergoes a reversible hypsochromic shift of ultraviolet absorption maxima in basic media establishes its structure as the thiourethane, XV.



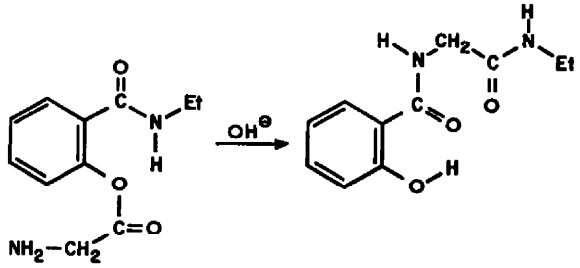
XIV XV XIII

Reaction of the benzisoxazolium salt with an aqueous solution of acetate ion generates in high yield a product of empirical formula $C_{11}H_{13}NO_3$ which is also obtained by reaction of ethylamine with *o*-acetoxybenzoylchloride. Since the IR spectrum of the substance shows carbonyl absorption at 5·63 μ and 5·99 μ, and since its NMR spectrum contains a methylene resonance which appears as a quintet, the acetate product must be formulated as O-acetyl-N-ethylsalicylamide, XVIa.



XVI$_a$ R=CH_3 XVII

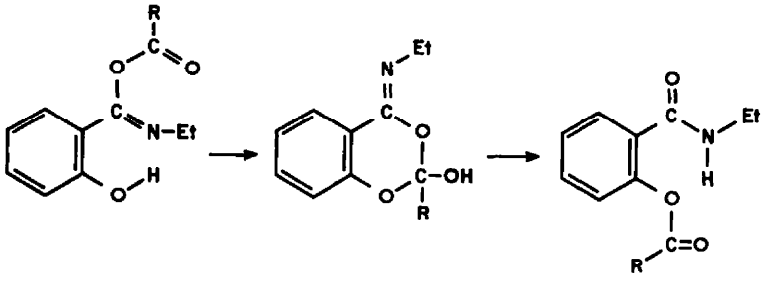
Other O-acyl-N-ethylsalicylamides are obtained by reaction of the benzisoxazolium salt with aqueous solutions of benzoate anion, methoxyacetate anion, and glycine. The glycine product (XVIb), which is best isolated as its picrate salt, undergoes the Brenner rearrangement[9] in aqueous alkaline solution, forming salicyloylglycine ethylamide, XVIII.



XVI$_b$ R=CH_2–NH_2 XVIII

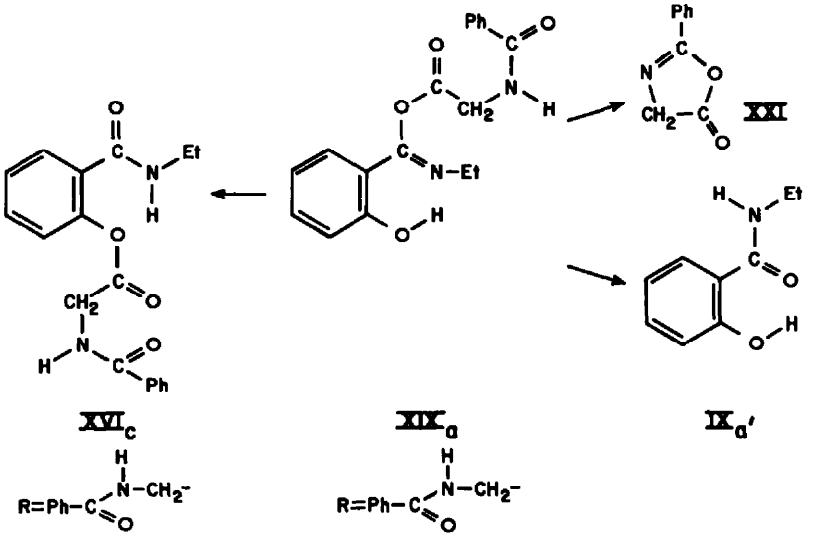
[9] M. Brenner, J. P. Zimmermann, J. Wehrmuller, P. Quitt, A. Hartmann, W. Schneider and U. Beglinger, *Helv. Chim. Acta* **40**, 1497 (1957).

The formation of O-acyl-N-ethylsalicylamides from the N-ethylbenzisoxazolium cation and carboxylate anions can best be rationalized as proceeding from an imino anhydride (XIX) by means of an acyl shift not dissimilar from that found by Titherley to occur with great facility in acyl salicylamides.[10] Although the imino anhydrides



XIX XX XVI

cannot be detected directly, indirect evidence for their intermediacy can be obtained from the reaction of the hippurate anion with the N-ethylbenzisoxazolium cation. While the major product of this reaction is the expected O-hippuryl-N-ethylsalicylamide (XVIc) a by-product identifiable by direct comparison as 2-phenyloxazol-5-one (XXI) is also formed. Since XVIc is stable to the reaction conditions and is in fact



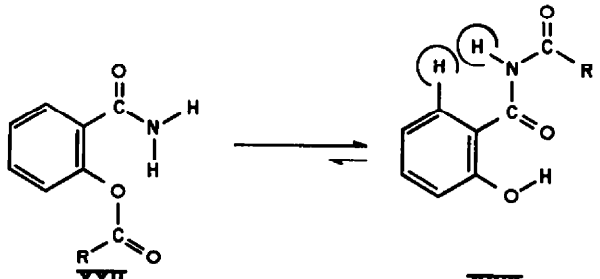
XVIc XIXa IXa'

formed by the base-catalyzed reaction of N-ethylsalicylamide (IXa') with 2-phenyloxazol-5-one, the latter substance must be formed from a more highly activated hippuryl derivative. A scheme involving an imino anhydride (XIXa) provides the simplest rationalization for these results.

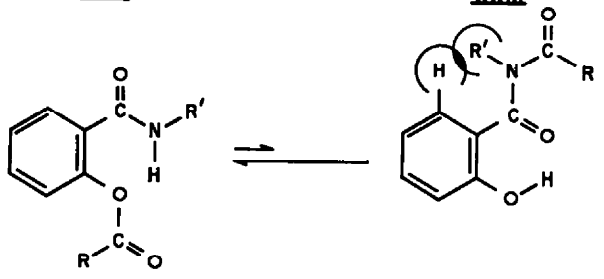
The stability of the O-acyl-N-ethylsalicylamides is a matter of considerable significance for the application of these substances to the synthesis of peptides. Should these substances undergo the ready O—N acyl migration described by Titherley[10] for simple O-acylsalicylamides, intramolecular imide formation could compete with the desired intermolecular acylation reaction. In fact, O-acetyl-N-ethylsalicylamide is

[10] J. McConnan and A. W. Titherley, *J. Chem. Soc.* 1333 (1906).

recovered in better-than 50% yield after it has been heated to 200° or refluxed for several hr in dry pyridine. The O-acyl-N-ethylsalicylamides prepared in this study are rapidly and completely saponified in aqueous media at pH 8–10. These findings stand in sharp contrast to the behavior of unsubstituted O-acylsalicylamides, which are rapidly and quantitatively converted to their N-acyl isomers under any of these reaction conditions. This striking effect of a single alkyl group can be given a simple steric rationalization. While the stable conformations of an O-acylsalicylamide are available to the corresponding O-acyl-N-alkylsalicylamide, as a consequence of steric interaction between the 6-hydrogen and N-alkyl grouping the planar, hydrogen-bonded conformation of an N-acylsalicylamide is not accessible to its N-alkyl derivative.



XXII XXIII



XXIV XXV

Reactions with thiourea

The general observations made on the reaction of the N-ethylbenzisoxazolium cation with an aqueous solution of thiourea are summarized in Chart II.

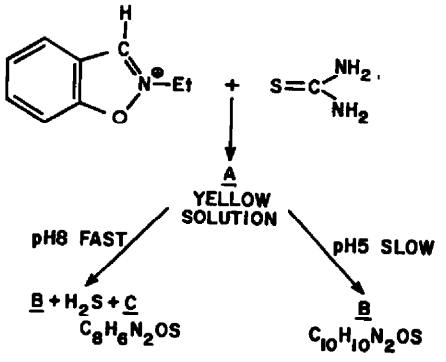
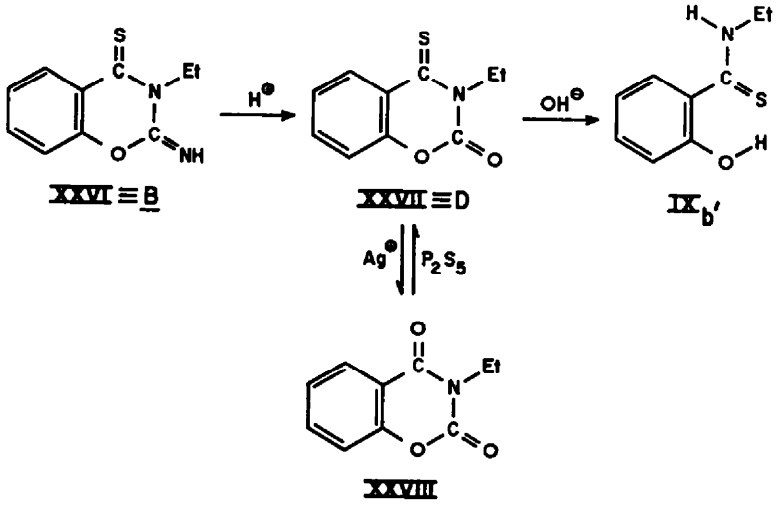


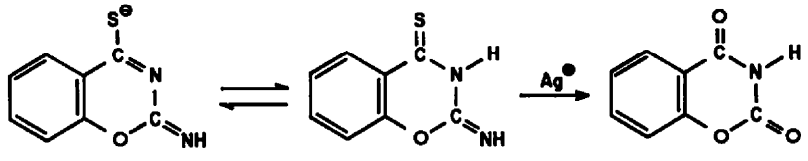
CHART II

Product *B*, obtainable as a brilliant-yellow solid from the slow decomposition of an initial product, is hydrolysed under acidic conditions to a markedly similar yellow substance, *D*, $C_{10}H_9NO_2S$, whose IR and NMR spectra imply the substitution of a carbonyl for an imino function. The alkaline hydrolysis of *D* yields *o*-hydroxy-N-ethylthiobenzamide (IXb′) while treatment of *D* with acidic silver nitrate solution generates 3-ethylbenzo[1,3]oxazin-2,4-dione (XXVIII). The latter transformation is reversed when XXVIII is fused with phosphorus pentasulphide. These transformations establish *D* as 3-ethyl-4-thiobenzo[1,3]oxazin-2,4-dione, (XXVII) and *B* as its imino derivative (XXVI).



XXVI ≡ B XXVII ≡ D IXb′ XXVIII

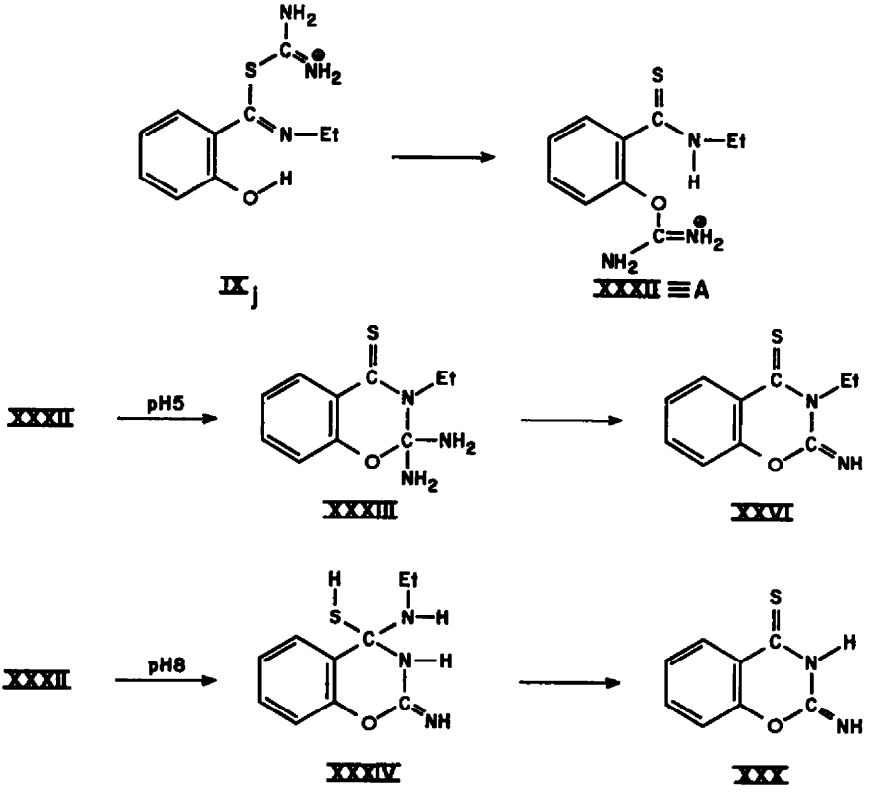
The spectroscopic data observed for *C* are in many respects similar to those observed for *B*, with the significant feature that *C* shows a reversible hypsochromic shift of ultraviolet absorption maxima in basic media. The formulation XXX fits these facts, an assignment which is confirmed by the conversion of *C* to benzo[1,3]-oxazin-2,4-dione (XXXI) by contact with acidic silver nitrate solution.



XXIX XXX ≡ C XXXI

Addition of picric acid to the clear, yellow solution containing *A* precipitates a salt of empirical formula $C_{16}H_{16}N_6O_8S$, reversibly convertible to a hydrochloride, and convertible in high yield to the products *B* and *C* in the appropriate buffered solutions. The salt is extremely unstable, decomposing to the product *B* and ammonium picrate during attempted recrystallization from acetonitrile. Despite its instability, an NMR spectrum of *A* can be obtained in a freshly prepared dimethyl sulphoxide solution containing hydrogen chloride. The methylene resonance of the substance appears as a quintet, a fact which proves the presence of a proton on the adjacent nitrogen atom

and strongly supports formulation XXXII for this substance. The two modes of intramolecular decomposition open to XXXII yield the products XXVI and XXX, while XXXII itself is probably derived from an initial imino intermediate (IXj) by an internal rearrangement analogous to that observed for the imino anhydrides of structure XIX.



Reactions with other nucleophiles

Although products were not examined in detail, a number of further reactions of the N-ethylbenzisoxazolium cation with nucleophiles were observed. Aniline combines in aqueous solution to yield a strongly basic substance, and phosphate anions to form polar species which are hydrolysed slowly at pH5 to N-ethylsalicylamide. Thiosulphate anion reacts to form an orange species which decomposes rapidly at pH 6 to a mixture of N-ethylsalicylamide and *o*-hydroxy-N-ethylthiobenzamide. All of these observations are consistent with the intermediacy of imines of general structure IX.

Attempts at inducing the combination of the benzisoxazolium cation with chloride, bromide, or iodide failed; the sole product of the attempted reactions in aqueous medium is N-ethylsalicylamide; and treatment of an acetone solution of sodium iodide and the benzisoxazolium salt with triethylamine yields an organic product which contains no replaceable iodine. While instability of imidohalides is a possible explanation, it seems likely that these results imply the indifference of the benzisoxazolium cation to halides other than fluoride.

Summary of results

In aqueous solutions within the pH range of 3 to 6 the N-ethylbenzisoxazolium cation combines at convenient rates with a wide variety of nucleophilic species. In each case the observed products may be regarded as derived from an imido derivative (IX) which with simple nucleophiles is the stable, isolable product. With more complex nucleophiles bearing electrophilic sites, the initial product (IX) can undergo internal rearrangements of which the thiourea conversions discussed above provide an illuminating example.

The broad reactivity of the N-ethylbenzisoxazolium cation is evidenced by its ability to combine with all nucleophilic elements of the first row of the periodic table and at least one member of the second. The products obtained from these transformations are formed rapidly and in most cases in very high yield. Their ready availability provides a bevy of unusual starting materials for the synthesis of new benzo-fused heterocyclic systems.

EXPERIMENTAL

IR spectra were measured with a Perkin–Elmer Infrared Model 137 spectrometer and calibrated by means of the 6·24 μ band of polystyrene. UV spectra were taken on a Cary Model 14 recording spectrophotometer; NMR spectra were taken on a Varian Associates Model A-60 spectrometer. Corrected m.ps were taken in pyrex capillary tubes, using a calibrated set of thermometers. Elemental analyses were performed by Scandinavian Microanalytical Laboratories of Copenhagen and by Dr. C. Daesslé of Montreal.

Benzisoxazole (VIII). A solution of 250 g (2·2 moles) hydroxylamine O-sulphonate[11] and 20 g Na_2SO_4 in 800 ml water was combined with 230 g (1·88 moles) salicylaldehyde in a 4 l. Erlenmeyer flask equipped with a sturdy mechanical stirrer. After a few min vigorous stirring the aldehyde dissolved and a few pearly crystals of the sodium salt of the oxime sulphonate separated. An additional 400 ml water and 400 ml CH_2Cl_2 were introduced, and the mixture was stirred vigorously and cooled in an ice-bath as $NaHCO_3$, 340 g (4·0 moles), was added in small portions. During the reaction a total of 300 ml water was added to reduce the viscosity of the suspension. When the addition was complete, the reaction mixture was stirred for 1 hr at room temp, or until the pearly crystals of the oxime sulphonate salt had disappeared. The two-phase suspension was transferred to a separatory funnel where the layers were separated. The aqueous solution was returned to the reaction flask along with 80 ml dichloromethane and 30 g $NaHCO_3$. The suspension was allowed to stir for 2 hr at room temp, whereupon the layers were separated, and the aqueous layer was extracted with five 30 ml portions of CH_2Cl_2. The CH_2Cl_2-extracts were pooled, dried over $MgSO_4$, and evaporated *in vacuo*. Vacuum distillation of the residual liquid yielded 212 g, 94·6%, benzisoxazole, b.p. 35–38° at 2 mm $n_D^{25°} = 1·5605$. The sample so obtained was identical in all respects with benzisoxazole prepared by the procedure of Lindemann.[12]

IR: $\lambda_{max}^{CCl_4}$ 6·22 μ (C=N stretch)

UV: $\lambda_{max}^{95\%EtOH}$ 235 (10,000), 243 (8,100), 280 mμ (2,900)

NMR: (neat) 1·2τ (1 proton, singlet) 2·3–3·0τ (4 protons, multiplet).

N-ethylbenzisoxazolium fluoborate. A solution of 55 g (0·46 mole) benzisoxazole and 87 g (0·46 mole) purified triethyloxonium fluoborate[13] in 200 ml CH_2Cl_2 was allowed to stand until crystals of the benzisoxazolium salt began to separate and then was cooled in ice to prevent loss of solvent. After 30 min the mixture was allowed to warm to room temp and to stand for 6 hr. The crystalline mass was broken up, collected, washed with CH_2Cl_2, and dried in the air to yield 104 g salt, 96%, m.p. 109·2–110·2°. A recrystallization from acetonitrile–ethyl acetate provides magnificant spars

[11] H. Matsuguma and L. F. Audrieth, *Inorganic Synthesis* (Edited by T. Moeller) Vol. V; p. 122. McGraw-Hill, New York (1957).

[12] H. Lindemann and H. Thiele, *Liebigs Ann.* **449**, 63 (1926).

[13] The crude oxonium salt obtained by Meerwein's procedure[8] was recrystallized by the addition of ether to a sat. CH_2Cl_2 solution of the salt.

m.p. 109·5–110·2°. The salt is not hygroscopic, although on long exposure to moist air it etches glass; it is slightly light-sensitive and should be stored in brown glass containers. (Found: C, 45·95; H, 4·58; N, 5·93. $C_9H_{10}NOBF_4$ requires: C, 46·00; H, 4·29; N, 5·96%.)

IR: $\lambda_{max}^{CH_2Cl_2}$ 6·20 μ (C=N stretch), 9–10 μ (BF_4^-)

UV: $\lambda_{max}^{H_2O}$ 258 (13,100), 297 mμ (2,900).

NMR: (CH_3CN) 0·2τ (1 proton, singlet), 1·8–2·4τ (4 protons, multiplet), 5·1τ (2 protons, quartet).

Hydrolysis of N-*ethylbenzisoxazolium fluoborate*

N-*Ethylsalicylamide* (IXa'). The solution obtained by dissolving 0·5 g (2 mmole) N-ethylbenzisoxazolium fluoborate in 20 ml 0·1 N HCl was heated to 90° on a steam bath for 3 hr. The resulting cloudy suspension was cooled and extracted with three 10 ml portions of CH_2Cl_2. The extracts were combined, dried over $MgSO_4$, and evaporated to yield 0·30 g solid, 90%, m.p. 55·0–56·5°; m.p. 56·8–57·5° after mixing with authentic N-ethylsalicylamide; reported m.p. for N-ethylsalicylamide: 58°.[14]

Reaction of the N-*ethylbenzisoxazolium cation with hydrosulphide anion*

o-*Hydroxy*-N-*ethylthiobenzamide* (IXb'). A solution of 40 g (0·17 mole) Na_2S-hydrate in 50 ml water was treated with slightly more than 1 equiv. HCl and mixed with a solution of 5·0 g (0·021 mole) N-ethylbenzisoxazolium fluoborate in 5 ml acetonitrile. After 5 min the pale-yellow suspension was extracted with three 15 ml portions CH_2Cl_2. The extracts were pooled, dried over $MgSO_4$, and passed through a 5 cm column of silica gel. The yellow elutant was evaporated, and the residue crystallized from CCl_4–cyclohexane. A recrystallization from ethyl acetate–cyclohexane yielded a first crop, 0·4 g, of a by-product which was discarded, and a second crop, 1·7 g, of product with m.p. 59·8–60·8°. Two recrystallizations from CCl_4 followed by two sublimations raised the m.p. to 60·5–61·3°. (Found: C, 59·80; H, 6·13; N, 7·55; S, 17·64. $C_9H_{11}NOS$ requires: C, 59·63; H, 6·12; N, 7·73; S, 17·69%.)

UV: $\lambda_{max}^{H_2O,\,pH\,1-6}$ 264 mμ (9,300) $\lambda_{max}^{H_2O,\,pH11,\,rev.}$ 267 (7,800), 286 mμ (5,500)

NMR: (CCl_4) −1·3τ (1 proton, singlet), 1·4τ (1 proton, singlet), 2·3–3·3τ (4 protons, multiplet), 6·4τ (2 protons, quintet), 8·8τ (3 protons, triplet).

When a solution of the thioamide (XIb') in dichloromethane was shaken with $AgNO_3$ aq, Ag_2S was immediately precipitated. The organic layer yielded 80% N-ethylsalicylamide, m.p. 56·5–57·8° after recrystallization; mixture m.p. with authentic N-ethylsalicylamide, 56·7–58·0°.

Reaction of the N-*ethylbenzisoxazolium cation with fluoride ion*

o-*Hydroxy*-N-*ethylbenzimido fluoride* (IXc). A solution of 4 g KBr in 10 ml water was treated with 10 g (41 mmoles) N-ethylbenzisoxazolium fluoborate. After 10 min the precipitated potassium fluoborate was collected, and KF, 15 g (0·13 mole), was added to the filtrate. The resulting suspension was extracted 3 times at 5 min intervals with 20 ml portions CH_2Cl_2. The resulting extracts were pooled, dried over Na_2SO_4 (*not* $MgSO_4$!), and evaporated. The residual liquid was taken up in pentane, and the resulting solution was filtered through a mixture of NaF and Celite and evaporated. The residual oil was distilled to yield 5·4 g, 76% of a colourless oil, b.p. 42–44° at 1 mm, which gives a positive fluoride reaction with zirconium alizirinate paper.[15] After two recrystallizations from pentane at −70° and a distillation the substance had b.p. 42–44° at 1 mm and $\eta_D^{25°} = 1·5312$. (Found: C, 64·32; H, 6·12; N, 8·52. $C_9H_{10}NOF$ requires: C, 64·65; H, 6·03; N, 8·38%.)

The iminofluoride has a piercing, mint-like odour, and severe headache can result from mild exposure to its vapours. Although it is rapidly decomposed when exposed to moisture or certain metallic salts, the substance appears to be indefinitely stable in the pure condition. It solidifies to a nicely crystalline solid at roughly −50°.

IR: $\lambda_{max}^{CCl_4}$ 3·0–3·7 μ (detailed and characteristic hydrogen stretch), 5·93 μ (C=N stretch)

NMR: (neat) −1·8τ (1 proton, singlet), 2·5–3·4τ (4 protons, multiplet), 6·5τ (2 protons, quartet), 8·8τ (3 protons, triplet).

Aqueous saponification of a sample of the iminofluoride with 0·1 N NaOH yielded N-ethylsalicylamide, m.p. 56·0–56·8°.

[14] *Beilstein's Handbuch der Organischen Chemie* Vol. X; p. 89. J. Springer, Berlin (1927).

[15] F. Feigl, *Spot Tests in Inorganic Analysis* (Fifth English Edition) p. 269. Elsevier, New York (1958).

Reaction of the N-*ethylbenzisoxazolium cation with cyanide ion*

o-*Hydroxy*-N-*ethylbenzimido nitrile* (IXd). NaCN, 5 g (0·1 mole), was dissolved in 20 ml water, and an overlayer of 10 ml n-pentane was added. The suspension was stirred vigorously while a solution of 2·0 g (0·0085 mole) N-ethylbenzisoxazolium fluoborate in 5 ml acetonitrile was added. The layers were separated, and the aqueous layer was extracted with two 10 ml portions n-pentane. The extracts were pooled, dried over $MgSO_4$, and evaporated, yielding 1·2 g 80%, bright-orange crystals, m.p. 43·0–45·0°. After 2 recrystallizations from n-pentane and 2 sublimations the substance melted in the range 45·0–45·7°. (Found: C, 68·92; H, 6·11; N, 16·36. $C_{10}H_{10}N_2O$ requires: C, 68·94; H, 5·79; N, 16·08%.)

IR: (CCl_4) 3·0–3·7 μ (characteristic hydrogen stretch), 4·48 μ (C≡N stretch), 6·16 μ (C=N stretch).

NMR: (CCl_4) −2·6τ (1 proton, singlet), 2·0–3·0τ (4 protons, multiplet), 6·0τ (2 protons, quartet), 8·6τ (3 protons, triplet).

Aqueous saponification of a sample of the nitrile using 0·1 N NaOH yields N-ethylsalicylamide (IXa), m.p. 56·8–57·8°; mixture m.p. 56·9–58·2°. Acidic hydrolysis in 48% HBr at room temp for 3 days yields *o*-hydroxyphenylglyoxylic acid (X), m.p. 39·5°; mixture m.p. 39·3°; reported m.p. 41–42°.[16]

Reaction of the N-*ethylbenzisoxazolium cation with methoxide ion*

Methyl o-*hydroxy*-N-*ethylbenzimidate* (IXe). A solution of 6·0 g (0·025 mole) N-ethylbenzisoxazolium fluoborate in 150 ml absolute MeOH was stirred vigorously during the addition of a solution of MeONa prepared by dissolving 0·60 g Na in 40 ml MeOH. When the addition was complete the solvent was evaporated *in vacuo*, and the residue was triturated 4 times with 20 ml portions n-pentane. The residue obtained by evaporating the pentane extracts was evaporatively distilled at 60°, 0·1 mm, yielding 3·0 g, 66%, of a bright-yellow oil which decomposes slowly at room temp. Three crystallizations from chilled pentane solutions gave a product which boiled in the range 90·0–92·0° at 0·1 mm. (Found: C, 66·56; H, 7·33; N, 7·74. $C_{10}H_{13}NO_2$ requires: C, 67·02; H, 7·31; N, 7·81%.)

IR: (CCl_4) 3·0–3·7 μ (characteristic hydrogen stretch), 6·10 μ (C=N stretch)

NMR: (CCl_4) 0·1τ (1 proton, singlet), 2·4–3·4τ (4 protons, multiplet), 6·5τ (5 protons, singlet and quartet), 8·8τ (3 protons, triplet)

Reaction of the N-*ethylbenzisoxazolium cation with azide ion*

o-*Hydroxy*-N-*ethylbenzimidoazide* (IXf) *and* 1-*ethyl*-2-(2-*hydroxyphenyl*)*tetrazole* (XII). A solution of 1·0 g (4·1 mmoles) N-ethylbenzisoxazolium fluoborate in 2 ml acetonitrile was added to a stirred, ice-cold solution of 2 g (0·03 mole) sodium azide in 25 ml water. The resulting yellow suspension was rapidly extracted with two 10 ml portions cold CCl_4. The organic layers were quickly combined, dried over $MgSO_4$, and cooled to −10°. An IR spectrum taken on this lemon-yellow solution showed absorption in the range 3·0–3·7 μ characteristic of the *o*-hydroxy-N-ethylbenzimido framework, azide absorption at 4·70 μ, and imine absorption at 6·1 μ. After 30 min at room temp the yellow colouration of the solution had disappeared, and a white solid had separated, m.p. 140·0–141·2°. After 2 recrystallizations from ethyl acetate the substance melted in the range 140·2–141·2°. (Found: C, 56·73; H, 5·43; N, 29·48. $C_9H_{10}N_4O$ requires: C, 56·83; H, 5·30; N, 29·46%.)

UV: $\lambda_{max}^{H_2O,\ pH\ 2-7}$ 283 mμ (3,200) $\lambda_{max}^{H_2O,\ pH\ 13,\ rev.}$ 308 mμ (4,500)

Reaction of o-*hydroxy*-N-*ethylbenziminofluoride* (IXc) *with ammonium hydroxide*

o-*Hydroxy*-N-*ethylbenzamidine* (XVII, IXh). A mixture of *o*-hydroxy-N-ethylbenziminofluoride, 0·5 g (3·0 mmoles), and 10 ml conc. NH_4OH was stirred vigorously at room temp for 4 hr. The precipitated product was collected by filtration, washed with CH_2Cl_2, and recrystallized from acetonitrile to yield 210 mg, 42%, of a white crystalline solid. Two recrystallizations from acetonitrile yielded a specimen with m.p. of 209°. (dec). (Found: C, 65·65; H, 7·45; N, 16·94. $C_9H_{12}N_2O$ requires: C, 65·84; H, 7·36; N, 17·05%.)

UV: $\lambda_{max}^{H_2O,\ pH\ 7-11}$ 340 mμ (6,900) $\lambda_{max}^{H_2O,\ pH\ 3,\ rev.}$ 288 mμ (2,800).

The substance forms a picrate salt from which it is regenerated by base.

[16] A. Baeyer and P. Fritsch, *Ber. Dtsch. Chem. Ges.* **17**, 973 (1884).

Reaction of the N-*ethylbenzisoxazolium cation with cyanate ion*

4-*Ethyliminobenzo*[1,3]*oxazin*-2,4-*dione* (XIII). A solution of 2·0 g (8·5 mmoles) N-ethylbenzisoxazolium fluoborate in 3 ml acetontirile was added to a solution of 10 g NaCNO in 25 ml water. The resulting milky suspension was extracted with three 10 ml portions CH_2Cl_2, and the extracts were pooled, dried over $MgSO_4$, and evaporated. The residue was recrystallized from acetonitrile to yield 1·3 g, 80%, of a white, crystalline solid, m.p. 193·5–194·0°. (Found: C, 63·12; H, 5·45; N, 14·71. $C_{10}H_{10}N_2O$ requires: C, 63·14; H, 5·30; N, 14·73%.)

IR: $\lambda_{max}^{CH_2Cl_2}$ 2·88 μ, 3·01 μ (N—H stretch), 5·79 μ (C=O stretch), 6·18 μ (C=N stretch)

UV: $\lambda_{max}^{H_2O,\ pH\ 1-10}$ 249 (16,600), 297 mμ (4,500)

NMR: (DMSO) 1·9–3·0τ (4 protons, multiplet), 6·4τ (2 protons, quartet), 8·8τ (3 protons, triplet).

Addition of a MeOH-solution of the cyanate product to NaOH aq resulted in the formation in high yield of *o*-hydroxy-N-ethylbenzamidine (IXh), m.p. 209° (dec), mixture m.p. 207·5–208·0° (dec); m.p. of picrate, 151·5–152·5°, mixture m.p. 150·0–151·0°.

Reaction of the N-*ethylbenzisoxazolium cation with thiocyanate ion*

2-*Thio*-4-*ethyliminobenzo*[1,3]*oxazin*-2,4-*dione* (XV). A solution of 2·0 g (8·5 mmoles) N-ethylbenzisoxazolium fluoborate in 3 ml acetonitrile was added to 25 ml of a 20% solution of NaCNS. The resulting turbid yellow mixture was extracted thrice with 10 ml portions CH_2Cl_2; the extracts were pooled, dried over $MgSO_4$, and evaporated. The resulting residue was recrystallized from $CHCl_3$ to yield 1·40 g, 80%, of nicely formed, pale-yellow prisms, m.p. 206·0–207·0°. Three recrystallizations from $CHCl_3$ raised the m.p. to 207·8–208·0°. (Found: C, 58·23; H, 4·96; N, 13·48; S, 15·57. $C_{10}H_{10}N_2OS$ requires: C, 58·23; H, 4·89; N, 13·58; S, 15·55%.)

IR: $\lambda_{max}^{CH_2Cl_2}$ 2·85 μ, 3·02 μ (N—H stretch), 6·22 μ (C=N stretch)

UV: $\lambda_{max}^{H_2O,\ pH\ 1-6}$ 259 (12,300), 288 (12,300), 297 (15,000), 325 mμ (8,400) $\lambda_{max}^{H_2O,\ pH\ 11,\ rev.}$ 250 (10,700), 290 (12,700), 297 mμ (13,300)

NMR: (DMSO) 1·8–2·9τ (4 protons, multiplet), 6·3τ (2 protons, quartet), 8·8τ (3 protons, triplet).

Addition of the thiocyanate product to a methanolic solution of $AgNO_3$ resulted in the formation in high yield of the cyanate product (XIII). After two recrystallizations from acetonitrile a specimen of m.p. 190·5–192·5° was obtained; mixture m.p. 192·5–193·5°.

Reaction of the N-*ethylbenzisoxazolium cation with acetate ion*

o-*Acetyl*-N-*ethylsalicylamide* (XVIa). A solution of 2 g sodium acetate in 15 ml water was brought to pH 5·5 by the addition of dil. HCl aq and stirred as 1·0 g (4·3 mmoles) N-ethylbenzisoxazolium fluoborate was added slowly as a fine powder. The milky mixture was extracted with three 5 ml portions CH_2Cl_2. The extracts were pooled, extracted with two 10 ml portions 0·5 N $NaHCO_3$, dried over $MgSO_4$, and evaporated. The residue was crystallized from CH_2Cl_2–cyclohexane to yield 0·75 g, 85%, of a white, waxy solid, m.p. 54·0–55·2°. Several recrystallizations from ethyl acetate–cyclohexane raised the m.p. to 55·0–55·6°. (Found: C, 63·63; H, 6·34; N, 6·78. $C_{11}H_{13}NO_3$ requires: C, 63·75; H, 6·32; N, 6·76%.)

This substance was identical in all respects with the product obtained by the reaction of ethylamine with *o*-acetoxybenzoyl chloride, m.p. 54·2–55·2°, mixture m.p. 55·0–55·3°.

IR: $\lambda_{max}^{CCl_4}$ 2·90 μ (N—H stretch), 5·66 μ (ester C=O stretch), 5·99 μ (amide C=O stretch).

UV: $\lambda_{max}^{H_2O,\ pH\ 1-6}$ 265 mμ (800).

NMR: (CH_3CN) 2·4–3·1τ (5 protons), 6·7τ (2 protons, quintet), 7·8τ (3 protons singlet).

Reaction of the N-*ethylbenzisoxazolium cation with benzoate ion*

o-*Benzoyl*-N-*ethylsalicylamide* (XVId, R = Ph). Substitution of benzoic acid in the procedure given for the reaction with acetic acid provided an 88% yield of a white crystalline solid, m.p. 111·8–112·6°. Several recrystallizations from ethyl acetate–cyclohexane raised the m.p. to 112·1–112·6°. (Found: C, 71·08; H, 5·79; N, 5·35. $C_{16}H_{15}NO_3$ requires: C, 71·36; H, 5·61; N, 5·20%.)

IR: $\lambda_{max}^{CH_2Cl_2}$ 5·75 μ (ester carbonyl), 5·99 μ (amide carbonyl).

Reaction of the N-*ethylbenzisoxazolium cation with methoxyacetate ion*

o-*Methoxyacetyl*-N-*ethylsalicylamide* (XVIe, R = CH_3OCH_2). Substitution of methoxyacetic acid in the procedure given for reaction with acetic acid provided an 88% yield of a white, waxy solid, m.p. 57·5–58·3°. Several recrystallizations from ethyl acetate–cyclohexane raised the m.p. to 59·3–60·2°. (Found: C, 60·52; H, 6·39; N, 6·03. $C_{12}H_{15}NO_3$ requires: C, 60·74; H, 6·37; N, 5·90%.)

IR: $\lambda_{max}^{CCl_4}$ 5·60 μ (ester carbonyl), 5·98 μ (amide carbonyl)

UV: $\lambda_{max}^{H_2O\ pH\ 1-7}$ 265 mμ (950).

Reaction of the N-*ethylbenzisoxazolium cation with glycine*

o-*Glycyl*-N-*ethylsalicylamide* (XVIb). Finely powdered N-ethylbenzisoxazolium fluoborate, 3·0 g (13 mmoles), was added to a stirred solution of 5 g (0·071 mole) glycine in 50 ml water. After 5 min a solution of 2·5 g picric acid and 1 g glycine in 30 ml water was added, and the resulting precipitate was collected and dried overnight *in vacuo*. There was obtained 4·4 g, 77%, of a lemon-yellow, crystalline precipitate, m.p. 137·0–139·0° (dec). Four recrystallizations from acetonitrile raised the m.p. to 145·5–147·0° (dec). (Found: C, 45·18; H, 3·97; N, 15·70. $C_{17}H_{17}N_5O_{10}$ requires: C, 45·24; H, 3·80; N, 15·52%.)

IR: λ_{max}^{KBr} 5·63 μ (ester carbonyl).

Conversion of o-*glycyl*-N-*ethylsalicylamide* (XVIb) *to* N-*salicoylglycine ethylamide* (XVIII). N-ethylbenzisoxazolium fluoborate, 2·0 g (8·5 mmoles), was dissolved in a solution of 5 g glycine in 50 ml water. After 5 min stirring, the solution was brought to pH 8·5 by the addition of 1 N NaOH; at the same time 25 ml acetone was added. After 2 hr at room temp, the solution was evaporated to half its volume on a rotary evaporator. The resulting suspension was brought to pH 1 by the addition of 3 N HCl and extracted with three 15 ml portions ethyl acetate. The organic phases were pooled, extracted once with a 10 ml portion of freshly sat. Na_2SO_4 aq, dried over $MgSO_4$ and evaporated. The residue was extracted with CCl_4 to yield an insoluble residue of 0·50 g, 26%, crude amide, m.p. 143·0–150·0°. Several recrystallizations from ethyl acetate–cyclohexane raised the m.p. to 165·0–165·8°. (Found: C, 59·30; H, 6·55; N, 12·53. $C_{11}H_{14}N_2O_3$ requires: C, 59·44; H, 6·35; N, 12·61%.)

The amide obtained by this procedure was identical in all respects with a sample prepared by the reaction of *o*-acetoxybenzoyl chloride with excess glycine ethylamide.

Reaction of the N-*ethylbenzisoxazolium cation with hippurate ion*

o-*Hippuryl*-N-*ethylsalicylamide* (XVIc) *and* 2-*phenyloxazol*-5-*one* (XXI). Hippuric acid, 7·0 g (0·039 moles), was dissolved in 40 ml 1 N NaOH. The resulting solution was brought to pH 5 by the addition of dil. HCl aq and stirred rapidly while 7·0 g (0·030 mmoles) finely powdered N-ethylbenzisoxazolium fluoborate was added. The resulting suspension was extracted 3 times with 20 ml portions CH_2Cl_2 which were then pooled, dried over $MgSO_4$, and evaporated. Extraction of the resulting residue with four 5 ml portions boiling cyclohexane and evaporation of the extract produced a semi-crystalline residue whose IR spectrum was that of a mixture of N-ethylsalicylamide and 2-phenyloxazol-5-one. Two recrystallizations from abs. EtOH yielded 70 mg of a solid which was identical in all respects with authentic 2-phenyloxazol-5-one prepared by the procedure of Cornforth;[17] m.p. 89·5–90·2°, mixture m.p. 89·4–90·2°. Recrystallization of the residue of the cyclohexane extraction from ethyl acetate–cyclohexane yielded 8·0 g, 73%, of a fluffy, white solid, m.p. 85·5–87·0°. Several recrystallizations from CH_2Cl_2–ether raised the m.p. of this substance to 87·5–89·0. (Found: C, 66·06; H, 5·85; N, 8·74. $C_{16}H_{16}N_2O_4$ requires: C, 66·25; H, 5·56; N, 8·58%.)

IR: $\lambda_{max}^{CH_2Cl_2}$ 5·63 μ (ester carbonyl), 5·99 μ (amide carbonyl).

Reaction of the N-*ethylbenzisoxazolium cation with thiourea at pH* 5

Product B, 2-*imino*-4-*thiobenzo*[1,3]*oxazin*-2,4-*dione* (XXVI). A solution of 2·0 g (8·5 mmoles) N-ethylbenzisoxazolium fluoborate in 3 ml acetonitrile was added to a solution of 4 g thiourea in 50 ml water buffered with 0·1 g each sodium acetate and acetic acid. The resulting pale-yellow suspension was extracted at 15 min intervals with five 15 ml portions CH_2Cl_2. The extracts were

[17] J. W. Cornforth in *The Chemistry of Penicillin* p. 800. Princeton (1949).

pooled, dried over $MgSO_4$, and evaporated. The residue was extracted with two 8 ml portions boiling cyclohexane which were then filtered while hot through Celite and cooled to yield 1·15 g, 66%, of a nicely crystalline, canary-yellow solid, m.p. 78·0–82·0°. Two recrystallizations from cyclohexane and two sublimations raised the m.p. to 83·0–83·6°. (Found: C, 58·21; H, 4·89; N, 13·57; S, 15·42. $C_{10}H_{10}N_2OS$ requires: C, 58·23; H, 5·02; N, 13·58; S, 15·55%.)

IR: $\lambda_{max}^{CCl_4}$ 2·93 μ (N—H stretch), 5·99 μ (C=N stretch)

UV: $\lambda_{max}^{H_2O,\ pH\ 8\text{-}11}$ 277 (10,600), 320 mμ (13,200).

NMR: (CCl_4) 1·8–3·2τ (4 protons, multiplet), 3·4τ (1 proton, broad singlet), 5·4τ (2 protons, quartet), 8·7τ (3 protons, triplet).

Acidic hydrolysis of product B

Product D, *3-ethyl-4-thiobenzo*[1,3]*oxazin-2,4-dione* (XXVII). A solution of 0·50 g (2·4 mmoles) of the product *B* in 10 ml MeOH was heated to boiling and treated with 5 ml 3 N HCl. As the solution cooled, a substance crystallized which was collected, washed with 50% MeOH, and recrystallized from MeOH aq. There was obtained 0·40 g, 80%, of brilliant yellow cubes, m.p. 106·4–107·3°. Two recrystallizations from MeOH and two sublimations raised the m.p. to 107·0–107·4°. (Found: C, 57·86; H, 4·29; N, 6·69. $C_{10}H_9NO_2S$ requires: C, 57·95; H, 4·38; N, 6·76%.)

IR: $\lambda_{max}^{CCl_4}$ 5·67 μ (carbonyl)

UV: $\lambda_{max}^{H_2O,\ pH\ 1\text{-}9}$ 270 mμ (12,200), 328 mμ (12,200)

NMR: (CCl_4) 1·7–3·0τ (4 protons, multiplet), 5·5τ (2 protons, quartet), 8·8τ (3 protons, triplet).

Alkaline hydrolysis of the substance yielded *o*-hydroxy-N-ethylthiobenzamide, m.p. 60·0–60·8°; mixture m. p. 60·3–61·2°. Treatment of the substance with acidic $AgNO_2$ aq yielded O,N-carbonyl-N-ethylsalicylamide, m.p. 102·0–103·0°; mixture m.p. 104·5–106·5°; reported m.p. 107°.[18]

Conversion of 3-ethylbenzo[1,3]*oxazin-2,4-dione* (XXVIII) *to the acidic hydrolysis product* D. A mixture of 2·0 g (1·05 mmoles) O,N-carbonyl-N-ethylsalicylamide, prepared by the pyridine-catalyzed reaction of ethyl chlorocarbonate with N-ethylsalicylamide, and 1·2 g P_2S_5 (Eastman technical grade) was heated to 175° and triturated vigorously for 10 min at that temp. The mixture was cooled and lixiviated with several portions CH_2Cl_2. The extracts were combined, filtered, and evaporated, and the resulting residue was recrystallized from MeOH, yielding 1·4 g 65%, of yellow cubes, identical in all respects with the authentic product *D*, m.p. 100·0–100·8°. A recrystallization raised the m.p. to 104·0–105·2°, mixture m.p. 104·8–106·4°.

Preparation of the product C

2-Imino-4-thiobenzo[1,3]*oxazin-2,4-dione* (XXX). A solution of 3·0 g (13 mmoles) N-ethylbenzisoxazolium fluoborate in 3 ml acetonitrile was added to a solution of 4 g thiourea in 50 ml water containing 0·1 g each of sodium acetate and acetic acid. The solution was allowed to stand for 6 min, and then was subjected to two rapid extractions with 10 ml portions CH_2Cl_2. The aqueous layer was quickly brought to pH 8 with dil. NaOH aq. A heavy yellow precipitate formed immediately, and H_2S was released. The precipitate was collected, washed thoroughly with water and CH_2Cl_2, and dried to yield 0·80 g, 36%, of a bright yellow solid, insoluble in all but the most polar organic solvents, m.p. 175–205° (dec). (Found: C, 53·71; H, 3·45; N, 15·57; S, 17·94. $C_9H_8N_2OS$ requires: C, 53·91; H, 3·39; N, 15·72; S, 17·99%.)

IR: λ_{max}^{KBr} 2·97 μ (C—H stretch), 6·03 μ (C=N stretch)

UV: $\lambda_{max}^{H_2O,\ pH\ 5}$ 277 (8,500), 334 mμ (13,200) $\lambda_{max}^{H_2O,\ pH\ 11\ rev.}$ 277 (6,100), 321 mμ (9,300)

NMR: ($(CD_3)_2SO$) 1·3τ (1·5 protons, broad singlet), 1·6–2·8τ (4 protons, multiplet), 6·5τ (0·5 proton, singlet).

Treatment of this substance with warm, acidic $AgNO_2$ aq generated O,N-carbonylsalicylamide, m.p. 226–228°; mixture m.p. 224–226°; reported m.p. 227°.[18]

Isolation of the picrate salt of the cation XXXII = A. Finely powdered N-ethylbenzisoxazolium fluoborate, 5·0 g (21 mmoles), was added with stirring to a solution of 7 g recrystallized thiourea in 100 ml water. After 5 min the solution was extracted quickly with 30 ml CH_2Cl_2, and the aqueous layer was run from the separatory funnel into a saturated solution of picric acid in 50 ml 30% EtOH–water. After 5 min the fluffy yellow precipitate was collected, washed with water and CH_2Cl_2, and dried overnight *in vacuo*. The resulting crystalline picrate, 4·8 g, 50%, is stable as a solid but

[18] A. Einhorn and C. Mettler, *Ber. Dtsch. Chem. Ges.* **35**, 3652 (1902).

decomposes rapidly in solution. The substance decomposes without melting in the range 140–150°. (Found: C, 42·08; H, 3·65; N, 18·72; S, 6·93. $C_{16}H_{16}N_6O_8S$ requires: C, 42·48; H, 3·56; N, 18·59; S, 7·09%.)

IR: (hydrochloride salt) λ_{max}^{KBr} 5·87 μ (isouronium group)

UV: (hydrochloride salt) $\lambda_{max}^{H_2O,\ pH\ 0}$ 273 (7,600), 340 mμ (300)

NMR: (picrate salt in DMSO) −0·2τ (1 proton, broad singlet), 1·4τ (6 protons, singlet superimposed on broad singlet), 2·6τ (4 protons, close doublet), 6·3τ (2 protons, quintet), 8·8τ (3 protons, triplet).

Addition of the substance to an aqueous acetate buffer generated product *B*; addition to a bicarbonate buffer generated products *B* and *C* together with a trace of hydrogen sulphide.

Acknowledgment—We are indebted to the National Science Foundation and the National Institutes of Health for financial support for this work. One of us (D.S.K.) would like to acknowledge generous support by the Harvard Society of Fellows and The E. P. Kohler Fund.